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(21) International Application Number: PCT/US91/08586 (22) International Filing Date: 22 November 1991 (22.11.91) (30) Priority data: 631,139 20 December 1990 (20.12.90) US (60) Parent Application or Grant (63) Related by Continuation US 631,139 (CIP) Filed on 20 December 1990 (20.12.90) (71) Applicant (for all designated States except US): WARNER-LAMBERT COMPANY [US/US]; 2800 Plymouth Road, Ann Arbor, MI 48105 (US).		(72) Inventors; and (75) Inventors/Applicants (for US only) : HAYS, Sheryl, Jeanr [US/US]; 1080 Bandera Drive, Ann Arbor, MI 4810 (US). JOHNSON, Graham [GB/US]; 1130 Bander Drive, Ann Arbor, MI 48103 (US). LESCOSKY, L onard, Joseph [US/US]; 328 Fifth Street, Ann Arbo MI 48103 (US). MALONE, Thomas, Charles [US/US 45139 North Spring Drive, Canton, MI 48187 (US). NC VAK, Perry, Michael [US/US]; 3327 Burbank Driv Ann Arbor, MI 48105 (US). (74) Agents: THIERSTEIN, Joan; Warner-Lambert Compan 2800 Plymouth Road, Ann Arbor, MI 48105 (US) et a (81) Designated States: AT (European patent), AU, BE (Eucrpean patent), CA, CH (European patent), DE (Eucrpean patent), DK (European patent), ES (European p: tent), FI, FR (European patent), GB (European patent GR (European patent), IT (European patent), JP, KF LU (European patent), NL (European patent), NO, S (European patent), US. Published <i>With international search report.</i>
(54) Title: 2-ACYLAMIDO DERIVATIVES OF 3,4-DIHYDRO-3-OXO-QUINOXALINE HAVING PHARMACEUTICAL ACTIVITY (57) Abstract The present invention relates to novel 2-acylamide derivatives of 3,4-dihydro-3-oxo-quinoxaline useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions and methods of treatment therefor. The compounds of the present invention have activity as excitatory amino acid receptor mediators and, thus, are useful in the treatment of a wide range of neurodegenerative disorders including cerebrovascular disorders such as stroke.		

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2-ACYLAMIDO DERIVATIVES OF
3,4-DIHYDRO-3-OXO-QUINOXALINE
HAVING PHARMACEUTICAL ACTIVITY

5

BACKGROUND OF THE INVENTION

The present invention relates to novel
2-acylamides of 3,4-dihydro-3-oxo-quinoxaline useful
as pharmaceutical agents, to methods for their
production, to pharmaceutical compositions and to
methods of use therefor.

The compounds of the present invention are active
as mediators of excitatory amino acid receptors.

Such activity is useful in the treatment of
neurodegenerative disorders including cerebrovascular
disorders as well as in the treatment of
schizophrenia, Parkinson's disease, or epilepsy; and
as analgesics and anxiolytics.

Excessive excitation by neurotransmitters can
cause the degeneration and death of neurons. It is
believed that this degeneration is in part mediated by
the excitotoxic actions of glutamate and aspartate at
the N-methyl-D-aspartate (NMDA) receptor. This
excitotoxic action is responsible for the loss of
neurons in cerebrovascular disorders such as cerebral
ischemia or cerebral infarction known as at least part
of a range of conditions, such as thromboembolic or
hemorrhagic stroke, cerebral vasospasm, hypoglycemia,
cardiac arrest, status epilepticus, perinatal
asphyxia, anoxia such as from drowning, pulmonary
surgery and cerebral trauma.

There are no specific therapies for these
neurodegenerative diseases; however, compounds which
act specifically as antagonists of the NMDA receptor

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complex, either competitively or noncompetitively,
offer a novel therapeutic approach to these disorders:

R. Schwarcz and B. Meldrum, The Lancet 140
(1985);

5 B. Meldrum in "Neurotoxins and Their
Pharmacological Implications" edited by P. Jenner,
Raven Press, New York (1987);

D. W. Choi, Neuron 1:623 (1988).

10 Confirmation of the protective effects of
noncompetitive NMDA antagonists in various
pharmacological models of neurodegenerative disorders
have appeared in the literature:

J. W. McDonald, F. S. Silverstein, and
M. V. Johnston, Eur. J. Pharmacol. 140:359 (1987);

15 R. Gill, A. C. Foster, and G. N. Woodruff, J.
Neurosci. 7:3343 (1987);

S. M. Rothman, J. H. Thurston, R. E. Haubart,
G. D. Clark, and J. S. Soloman, Neurosci. 21:673
(1987);

20 M. P. Goldbert, P-C. Pham, and D. W. Choi,
Neurosci. Lett. 80:11 (1987);

L. F. Copeland, P. A. Boxer, and F. W. Marcoux,
Soc. Neurosci. Abstr. 14 (part 1):420 (1988);

J. A. Kemp, A. C. Foster, R. Gill, and
25 G. N. Woodruff, TIPS 8:414 (1987);

R. Gill, A. C. Foster, and G. N. Woodruff J.
Neurosci. 25:847 (1988);

C. K. Park, D. G. Nehls, D. I. Graham,
G. M. Teasdale, and J. M. McCulloch, Ann. Neurol.
30 24:543 (1988);

G. K. Steinburg, C. P. George, R. DeLaPlaz,
D. K. Shibata, and T. Gross, Stroke 19:1112 (1988);

J. F. Church, S. Zeman, and D. Lodge,
Anesthesiology 69:702 (1988).

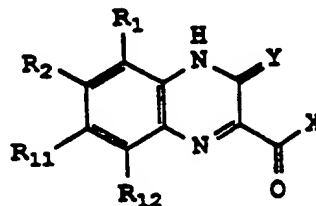
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U.S. Patent Number 4,181,724 discloses certain acids and esters of quinoxalinone compounds useful for asthma, eczema, or urticaria in animals. U.S. Patent Nos. 4,210,647 and 4,264,600 and European Patent Publication No. 010,426 disclose more specifically substitutions on acids and esters of quinoxalinone compounds that are useful as antivirals, especially against influenza viruses. The further preparation of these compounds is as in Japanese application 1075-474-A described in Derwent Abstract No. 89-132587/18. Quaternary ammonium salts of certain acids of quinoxalinone compounds are also disclosed as antivirals in U.S. 4,252,954. Amido derivatives of quinoxalinones are substituents of alkylarylsulfonylureas for use in hypoglycemia in Belgium Patent No. 764,998 and also are substituents of cephalosporins for use as antibacterials in European Application No. 304,158.

Each of these references differs from the present invention by the hydroxamate; amide; acyl urea; acyl carbamate; imide; acyl sulfonamide; or hydrazine derivatives of the quinoxalinone as disclosed herein.

SUMMARY OF THE INVENTION

The present invention provides compounds of the formula



I

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or tautomers thereof; or a pharmaceutically acceptable base or acid addition salt thereof; wherein

(1) Y is oxygen or sulfur;

(2) R_1 , R_2 , R_{11} , and R_{12} are independently
 5 hydrogen, lower alkyl, halogen, trifluoromethyl, cyano, nitro, methylthio, lower alkenyl, lower alkynyl, SO_2NH_2 , $S(O)_{1-2}R$ wherein R is hydrogen or lower alkyl, OCF_3 , or two of R_1 , R_2 , R_{11} , and R_{12} can be taken together to form a carbocyclic ring
 10 of six carbons, or can be taken together to form a heterocyclic or heteroaryl ring wherein the heteroatom is oxygen, sulfur, or nitrogen, and wherein the carbon on the carbocyclic ring is optionally further substituted by one of R_1 , R_2 ,
 15 R_{11} , or R_{12} ;

(3) X is

(a) $NR^6SO_2R^3$,

(b) NR^6R^3 with the proviso that one of R^6 and R^3 must be other than hydrogen and at
 20 the same time one of R_1 , R_2 , R_{11} , and R_{12} must be other than hydrogen,

(c) NR^6OR^3 ,

(d) $NR^6CONR^3R^4$ with the proviso that one of R^3 and R^4 must be other than hydrogen,

(e) NR^6COR^5 ,

(f) $NR^6CO_2R^3$,

(g)
$$\begin{array}{c} R_6H \\ | \\ N-N-CO_2R^3 \end{array}$$

(h)
$$\begin{array}{c} R_6H \\ | \\ N-N-SO_2R^3 \end{array}$$

(i) an amino acid residue which is phenylglycine, phenylalanine, alanine,
 35 leucine, isoleucine, proline, or valine,

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(j) lower alkyl esters of the amino acid residue as defined above;

wherein

- 5 i) R^3 and R^4 are independently
- 1) hydrogen;
 - 2) alkyl of from one to
20 twenty carbons, preferably one to
twelve carbons;
 - 3) alkenyl of from three to
twenty carbons, preferably three
to twelve carbons;
 - 4) alkynyl of from three to
twenty carbons, preferably three
to twelve carbons;
 - 15 5) aryl which is phenyl,
indenyl, or naphthyl wherein
phenyl is
 - aa) unsubstituted or
 - bb) substituted by one to
20 five of lower alkyl or
halogen, or
 - cc) substituted by one to
three of
 - xxi) trifluoromethyl,
 - 25 xxii) nitro,
 - xxiii) amino,
 - xxiv) mono- or di-lower
alkylamino,
 - xxv) hydroxy,
 - 30 xxvi) lower alkoxy,
 - xxvii) carboxy, or
 - xxviii) NHCOR^5 wherein R^5
is independently as
defined below,

35

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5

O
|

xxix) NHCOAlk_{1-6} wherein
 Alk_{1-6} is lower alkyl,
xxx) NHSO_2R^5 wherein R^5
is independently as
defined herein,

10

xxxi) CN,
xxxii) CONR^5R^6 wherein R^5
and R^6 are independently
as defined herein,
xxxiii) $\text{S}(\text{O})_{0-2}\text{R}^5$ wherein
 R^5 is independently
defined herein,

15

O
|

xxxiv) $-\text{CR}^5$;

20

- 6) arylloweralkyl;
7) arylloweralkenyl;
8) heterocycle;
9) heteroaryl;
10) $(\text{CH}_2)_q\text{R}^7$ wherein q is an
integer of one to four and R^7 is

25

- (A) heterocycle,
(B) heteroaryl,
(C) SO_2R^8 wherein R^8 is
hydrogen or lower alkyl and R
is independently as defined
herein,

30

- (D) PO_3R^8 wherein R^8 is as
defined above,

- (E) CO_2R^8 wherein R^8 is as
defined above, or

35

- (F) NR^9R^{10} wherein R^9 and R^{10}
are independently hydrogen or

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alkyl or R^9 and R^{10} are taken together to form a heteroaryl ring; or

11) an amino acid residue as defined above;

ii) R^5 is

- 1) hydrogen,
- 2) lower alkyl,
- 3) lower alkenyl,
- 4) aryl,
- 5) arylloweralkyl,
- 6) arylloweralkenyl,
- 7) heteroaryl or
- 8) heteroarylloweralkyl;

iii) R^6 is

- 1) hydrogen or
- 2) lower alkyl, preferably hydrogen.

The preferred compounds of the present invention include but are not limited to the compounds of Formula I wherein R_2 and R_{11} are chloro, Y is oxygen, and X is $NHS(O)_2CH_3$, $NHS(O)_2phenyl$, or $NHS(O)_2(CH_2)_4H$.

The more preferred compounds of the present invention are 6,7-dichloro-3,4-dihydro-3-oxo-N-[phenylsulfonyl]-2-quinoxalinecarboxamide and 6,7-dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxalinecarboxamide.

The present invention also includes a pharmaceutical composition for the use of treating cerebrovascular disorders, treating disorders responsive to the blockade of glutamic and aspartic acid receptors, or treating cerebral ischemia, cerebral infarction, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, cerebral trauma, schizophrenia, epilepsy, neurodegenerative disorders,

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Parkinson's disease, Alzheimer's disease, or Huntington's disease comprising a therapeutically effective amount of a compound of Formula I together with a pharmaceutically acceptable carrier.

5 The present invention also includes a method for treating cerebrovascular disorders which comprises administering to a patient in need thereof the above pharmaceutical composition in unit dosage form.

10 The present invention also includes a method for treating disorders responsive to the blockade of glutamic and aspartic acid receptors comprising administering to a patient in need thereof a therapeutically effective amount of the above composition in unit dosage form.

15 The invention also includes a method for treating cerebral ischemia, cerebral infarction, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, cerebral trauma, schizophrenia, epilepsy, neurodegenerative disorders, Parkinson's disease,
20 Alzheimer's disease, or Huntington's disease comprising administering to a patient in need thereof a therapeutically effective amount of the above composition in unit dosage form.

25 The invention also includes a method for treating stroke in patients in need thereof which comprises administering to a patient in need thereof a therapeutically effective amount of the above composition in unit dosage form.

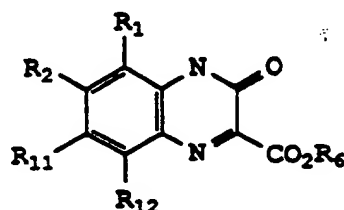
30 The invention also includes using as an anesthetic or using together with an anesthetic the above composition in surgical operations where a risk of cerebrovascular damage exists.

35 The invention further includes processes for the preparation of compounds of Formula I wherein one of the novel intermediates of the Formula II' wherein R_6

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is hydrogen are treated to obtain selected corresponding compounds of the Formula I. Further, the compounds of the Formula IV are treated to obtain compounds of Formula I.

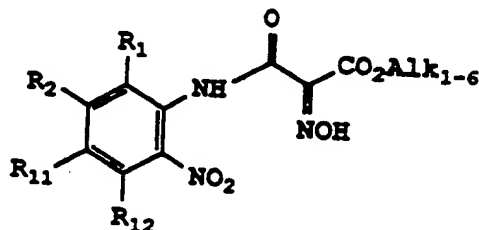
The invention still further includes novel intermediates useful in the processes. The novel intermediate of the present invention is a pure compound of the formula (II')



II'

wherein R₁ and R₁₁ are as defined above with the proviso that R'₂ and R'₁₂ are independently hydrogen or halogen with the proviso that at least one of R'₂ and R'₁₂ are halogen, and R₆ is as defined herein.

A novel intermediate of the present invention is also a compound of the Formula V

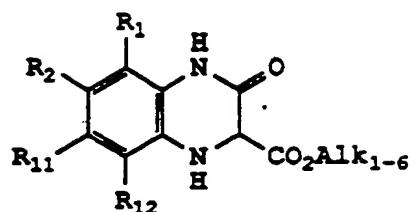


V

wherein R₁, R₂, R₁₁, and R₁₂ are as defined above and Alk₁₋₆ is lower alkyl.

An additional novel intermediate of the present invention is a compound of the Formula (IV)

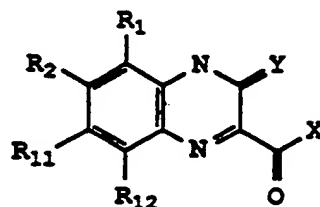
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IV

wherein R₁, R₂, R₁₁, R₁₂, and Alk₁₋₆ are as defined above.

Further, the present invention is a process for the preparation of a compound of the Formula (L)

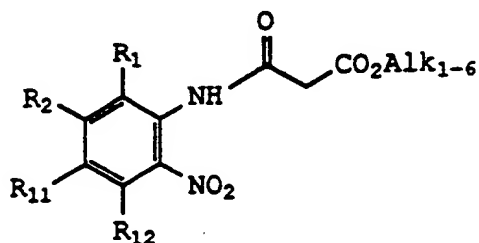


L

wherein R₁, R₂, R₁₁, R₁₂, X, and Y are as defined above.

The present invention is a process which comprises

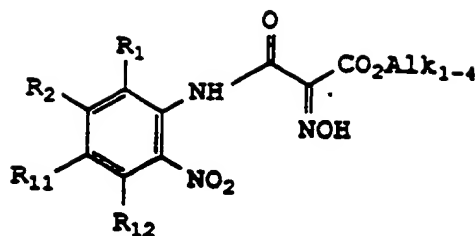
- 1) treating a compound of the Formula (VI)



VI

with sodium nitrite to obtain a compound of the Formula V

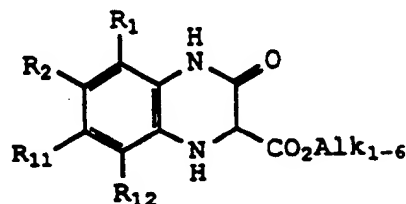
-11-



V

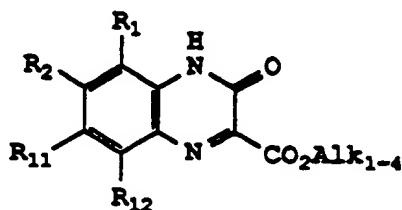
then

2) treating the compound of the Formula V of Step 1) with hydrogen over Raney nickel and then with TiCl_3 to obtain a compound of the Formula IV.



IV

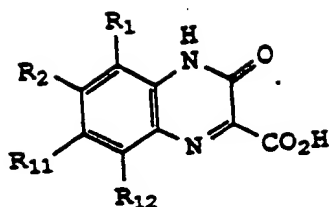
3) treating the compound of the Formula IV of Step 2) with n-bromosuccinimide, bromine, NaOCl , or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DOQ) in an inert solvent to obtain a compound of the Formula (II'1)



II'1

4) hydrolyzing the compound of the Formula II'1 with a hydroxide such as sodium or potassium hydroxide; to obtain the compound of the Formula (II'2)

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II' ₂

wherein R_1 , R_2 , R_{11} , and R_{12} are as defined above and Alk_{1-6} is lower alkyl.

This process is shown in Scheme E hereinafter.

DETAILED DESCRIPTION

Loweralkyl means a straight chained or branched chain of from one to four carbon atoms including but not limited to methyl, ethyl, propyl, butyl.

Loweralkenyl means a group from two to four carbon atoms, for example, but not limited to ethylene, 1,2- or 2,3-propylene, 1,2- 2,3-, or 3,4-butylene.

Loweralkynyl means a group from two to four carbon atoms, for example, but not limited to ethynyl, 2,3-propynyl, 2,3-, or 3,4-butynyl; propynyl is the preferred group.

Cycloalkyl loweralkyl means cycloalkyl of from three to six carbon atoms and lower alkyl as above, meaning for example, cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl; cyclopropylmethyl is the preferred group.

Loweralkoxy means a group of from one to four carbon atoms, for example, but not limited to methoxy, ethoxy, propoxy; methoxy is the preferred group.

Halogen is fluorine, chlorine, bromine, or iodine; fluorine, chlorine and bromine are the preferred groups.

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5 Arylloweralkyl means aryl as defined above and alkyl as defined above, for example, benzyl, 2-phenylethyl, 3-phenylpropyl; preferred groups are benzyl and the benzyl or phenyl is as substituted above.

10 Arylloweralkenyl means aryl as defined above and alkenyl as defined above, for example, 2-phenylethenylenyl, 3-phenylpropenylenyl; preferred groups are 2-phenylethenylenyl and the phenyl is as substituted above.

Monoloweralkylamino means a group containing from one to four carbon atoms, for example, but not limited to methylamino, ethylamino, n- or i-(propylamino or butylamino).

15 Diloweralkylamino means a group containing from one to four carbon atoms in each lower alkyl group, for example, but not limited to dimethylamino, diethylamino, di-(n-propyl)-amino, di-(n-butyl)-amino, or may represent a fused ring, for example piperidine.

20 Heteroaryl means a 5- or 6-membered monocyclic, bicyclic, or fused bicyclic heteroaryl. The monocycle or fused bicyclic aromatic ring contains at least 1 to 4 heteroatoms in at least one ring, such as nitrogen, oxygen, or sulfur or a combination thereof. Such a
25 heteroaryl group includes, for example, thienyl, benzothienyl, furanyl, benzofuranyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, pyrrolyl, pyrazolyl, isothiazolyl, thiazolyl, oxazolyl, isoxazolyl, triazolyl, tetrazolyl, imidazolyl,
30 benzothiazolyl, indolyl, quinolinyl, isoquinolinyl, or N-oxides of heteroaryl containing a nitrogen atom.

More specifically, such a heteroaryl may be a 2- or 3-thienyl; which may further be substituted by, for example, a 2-, 3-, or 4-pyridyl ring; 2- or 3-furanyl;
35 2-, or 3-, or 4-pyridyl or -pyridyl-N-oxide; 2-, 4-,

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or 5-pyrimidinyl; 3- or 4-pyridazinyl; 2-pyrazinyl;
2-pyrazinyl-N-oxide; 2- or 3-pyrrolyl; 3-, 4-, or
5-pyrazolyl; 2-, 4-, or 5-oxazolyl; 2-, 4-, or
5-thiazolyl; 3-, 4-, or 5-isoxazolyl; 3-, 4-, or
5-isothiazolyl; 5-tetrazolyl; 3- or
5-(1,2,4,-)triazolyl; 4- or 5-(1,2,3-)triazolyl; 2-,
4-, or 5-imidazolyl; 2-, 3-, 4-, 5-, 6-, or 7-indolyl;
2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolinyl; 1-, 3-, 4-,
5-, 6-, 7-, or 8-isoquinolinyl; 2-, 4-, 5-, 6-, or
7-benzothiazolyl; 2-, 3-, 4-, 5-, 6-, or aryl,
7-benzothieryl 1,2-benzisoxazol-3-yl.

Heterocycle means piperidine, piperazine,
tetrahydropyridine, tetrahydropyranyl, pyrrolidinyl,
pyrazolidinyl, oxazolidinyl, tetrahydrofuranyl,
tetrahydrothienyl, and the like. Particularly
included are N-piperidine and N-piperazine, which may
be further substituted by phenyl.

Well-known protecting groups and their
introduction and removal may be used according to the
skill in the art and are described, for example, in
J. F. W. McOmie, Protective Groups in Organic
Chemistry, Plenum Press, London, New York (1973), and
T. W. Greene, Protective Groups in Organic Synthesis,
Wiley, New York (1981).

The compounds of the present invention contain
asymmetric carbon atoms. The instant invention
includes the individual diastereomers and enantiomers,
which may be prepared or isolated by methods known to
those skilled in the art.

Selected compounds of the present invention can
exist also as syn and anti forms and are also the
present invention.

Any resulting racemate can be resolved into the
optical antipodes by known methods, for example by
separation of the diastereomeric salts thereof, with

-15-

an optically active acid, and liberating the optically active amine compound by treatment with a base. Racemic compounds of the present invention can thus be resolved into their optical antipodes e.g., by

5 fractional crystallization of d- or l-(tartarates, mandelates, or camphorsulfonate) salts. The compounds of the instant invention may also be resolved by the formation of diastereomeric amides or amides by

10 reaction the compounds of the instant invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-)-camphanic acid or by the formation of diastereomeric carbamates by reaction of

15 the compounds of the instant invention with an optically active chloroformate or the like.

Additional methods for resolving optical isomers, known to those skilled in the art may be used, for example those discussed by J. Jaques, A. Collet, and S. Wilen in Enantiomers, Racemates, and Resolutions,

20 John Wiley and Sons, New York (1981).

Salts of the compounds of the invention are preferably pharmaceutically acceptable salts. The compounds of the invention are basic amines from which acid addition salts of pharmaceutically acceptable

25 inorganic or organic acids such as strong mineral acids, for example, hydrohalic, e.g., hydrochloric or hydrobromic acid; sulfuric, phosphoric or nitric acid; aliphatic or aromatic carboxylic or sulfonic acids, e.g., acetic, propionic, succinic, glycolic, lactic,

30 malic, tartaric, gluconic, citric, ascorbic, maleic, fumaric, pyruvic, pantoic, nicotinic, methanesulfonic, ethanesulfonic, hydroxyethanesulfonic, benzene-sulfonic, p-toluenesulfonic, or naphthalenesulfonic acid can be prepared.

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Selected compounds of the invention are also acids from which basic salts may be prepared.

Likewise, hydrates of compounds of the invention; for which hydrates may exist, are also the present invention.

5 The compounds of the instant invention exhibit valuable pharmacological properties by selectively blocking the N-methyl-D-aspartate sensitive excitatory amino acid receptors in mammals. The compounds are thus useful for treating diseases responsive to excitatory amino acid blockade in mammals.

10 Such disorders include but are not limited to cerebral ischemia or cerebral infarction resulting from a range of conditions such as thromboembolic or hemorrhagic stroke, cerebral vasospasm, hypoglycemia, cardiac arrest, status epilepticus, perinatal asphyxia, anoxia such as from drowning, pulmonary surgery, and cerebral trauma. Other treatments are for schizophrenia, epilepsy, spasticity,

15 neurodegenerative disorders such as Parkinson's disease, Alzheimer's disease or Huntington's disease, Olivo-pontocerebellar atrophy, spinal cord injury, and poisoning by exogenous NMDA poisons (e.g., some forms of lathyrism). Further uses are as analgesics and anesthetics, particularly for use in surgical

20 procedures where a finite risk of cerebrovascular damage exists.

25 The effects are demonstrable in in vitro tests or in vivo animal tests using mammals or tissues or enzyme preparations thereof, e.g., mice, rats, or monkeys. The compounds are administered to patients enterally or parenterally, for example, orally, transdermally, subcutaneously, intravenously, or intraperitoneally. Forms include but are not limited

30 to gelatin capsules, or aqueous suspensions or

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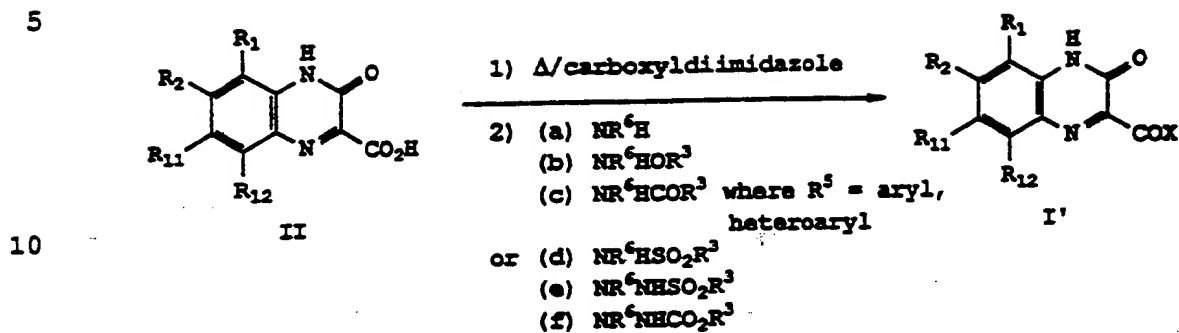
solutions. The applied in vivo dosage may range between about 0.01 to 100 mg/kg, preferably between about 0.05 and 50 mg/kg, most preferably between about 0.1 and 10 mg/kg.

5 Methods of synthesis of the compounds of the instant invention are illustrated in Schemes A, B, and C. The preparation of compounds of the Formula I' wherein X is $\text{NR}^6\text{SO}_2\text{R}^3$, NR^6R^3 , NR^6OR^3 , NR^6COR^5 , $\text{NR}^6\text{NHSO}_2\text{R}^3$, $\text{NR}^6\text{NHSO}_2\text{R}^3$, $\text{NR}^6\text{NHSO}_2\text{R}^3$ or $\text{NR}^6\text{NHSO}_2\text{R}^3$ and R_1 , R_2 , R^3 , R^4 , R^5 , and R^6 are as previously defined and are illustrated in Schemes A and B.

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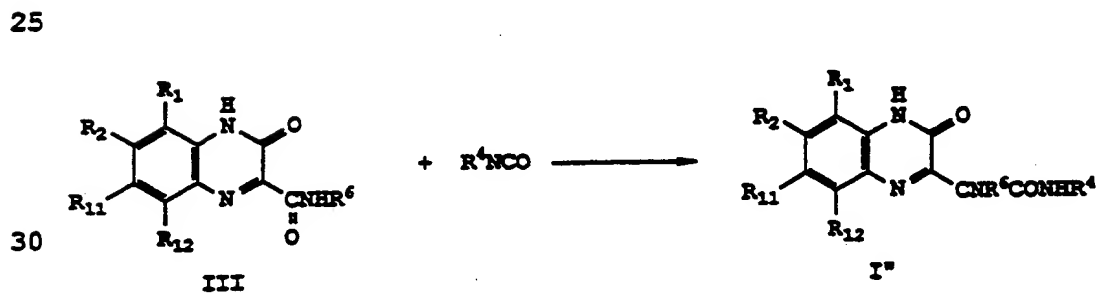
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Scheme A



Further, preparation of compounds of the Formula I wherein X is $\text{NHCONR}^3\text{R}^4$ and R^3 is H and R_1 , R_2 , R_{11} , R_{12} , and R^4 are as previously defined are illustrated in Scheme B.

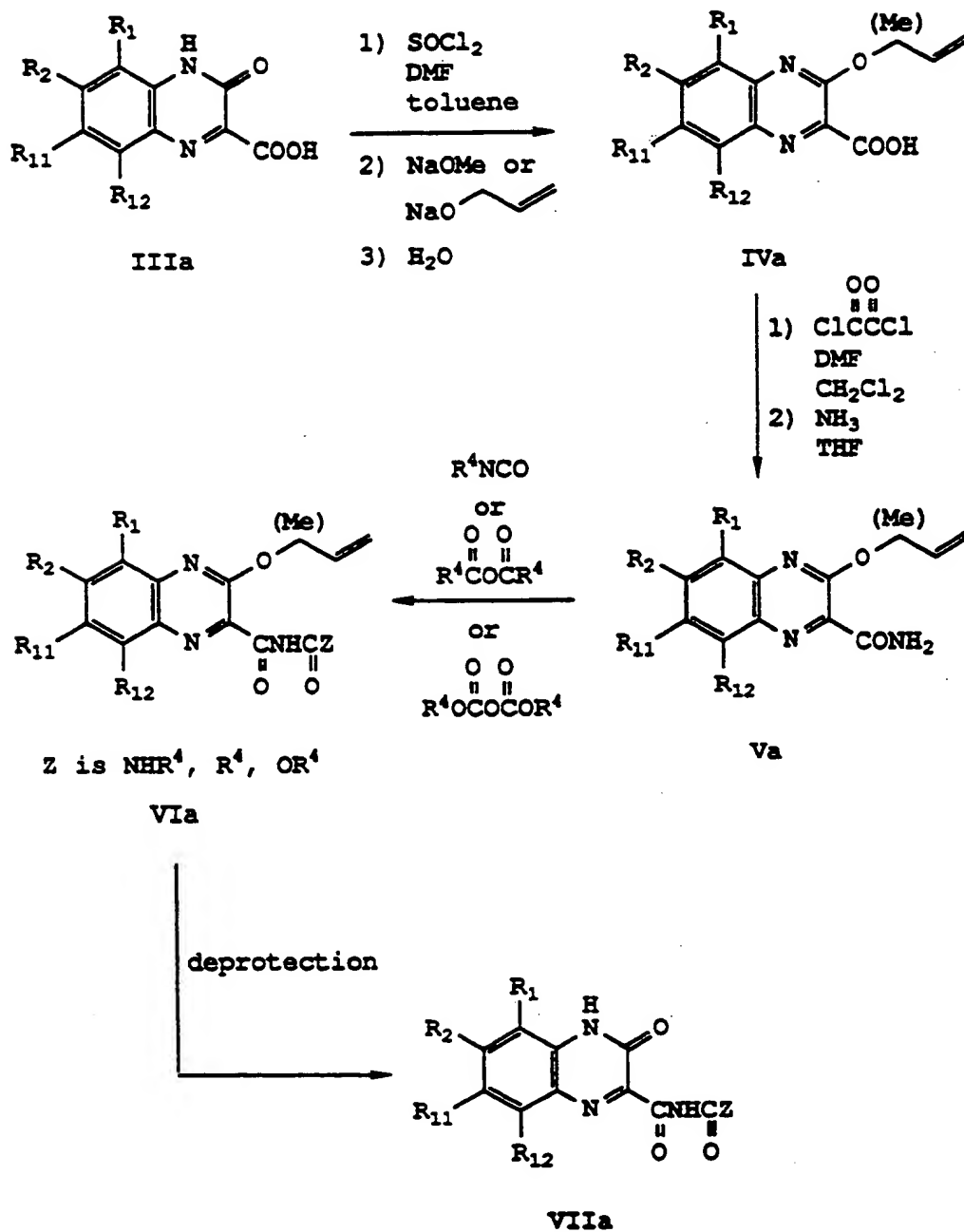
Scheme B



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The preferred method for making compounds of Formula I' is shown in Scheme C.

Scheme C

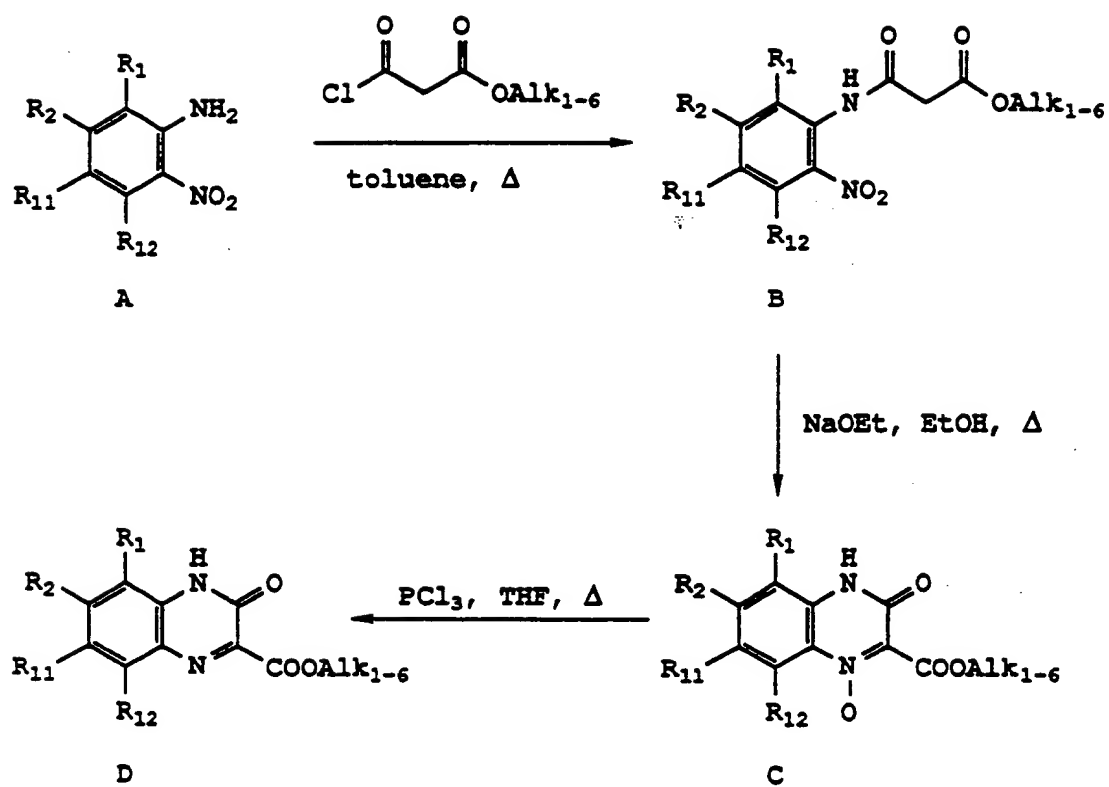


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Scheme D consists of treating the compounds of Formula A with chloroethylmalonate, chloromethylmalonate, or the like in a solvent such as benzene or toluene or the like to provide the compounds of the Formula B. The compounds of the Formula B are then treated with sodium ethoxide in ethanol or sodium methoxide in methanol to provide the compounds of the Formula C. The compounds of the Formula C are further reacted with phosphorous trichloride or phosphorous tribromide in a solvent such as tetrahydrofuran, dioxane, or the like to provide the compounds of the Formula D.

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Scheme D

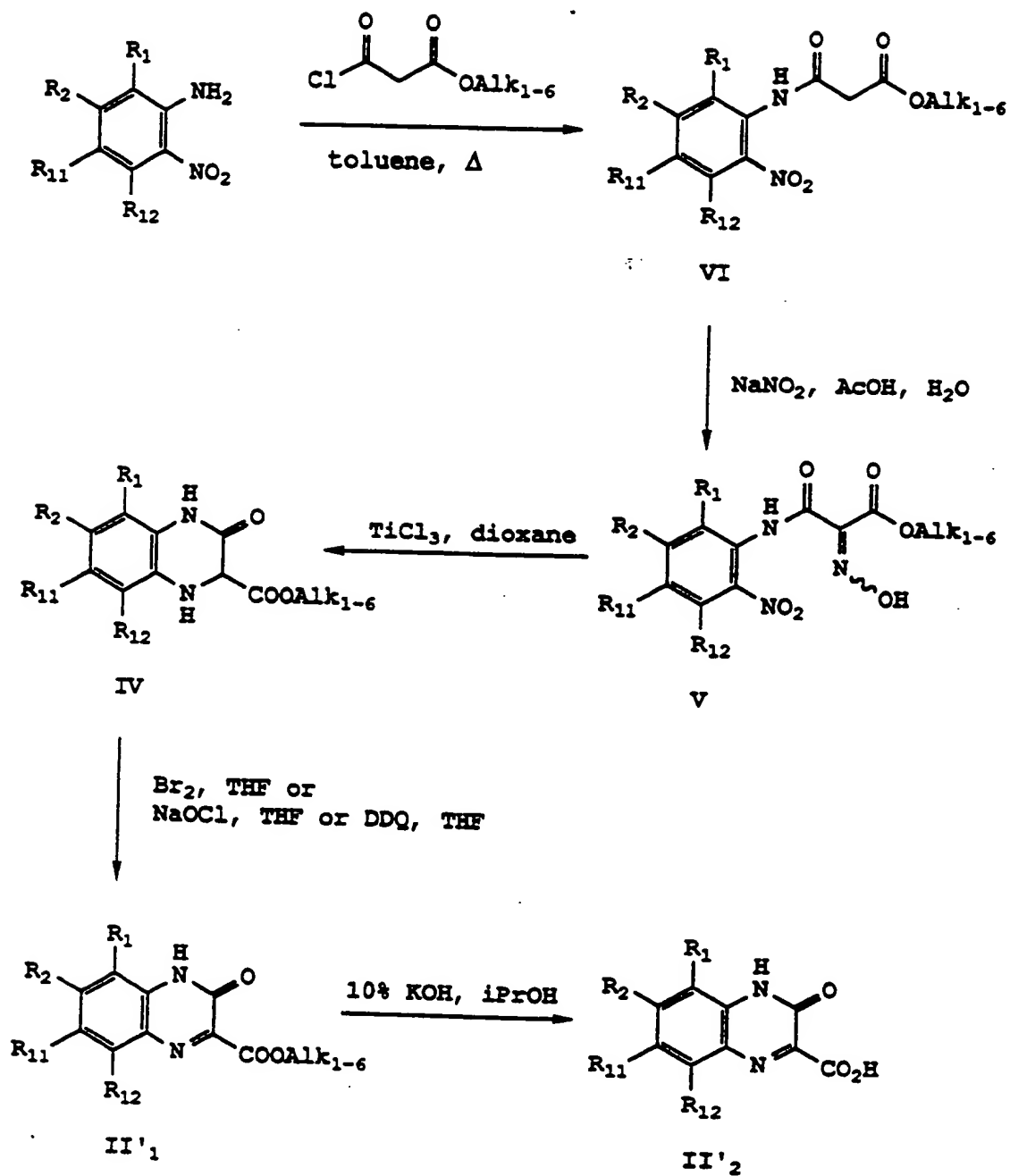


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Scheme E shows a preparation for compounds of the Formula I which consists of treating the compounds of the Formula VI with sodium nitrite, potassium nitrite, or the like in an acetic acid/tetrahydrofuran/water solvent mixture to provide the compounds of the Formula V. The compounds of the Formula V are then hydrogenated over Raney nickel in a solvent such as tetrahydrofuran or dioxane or the like, followed by treatment with aqueous titanium trichloride to provide the compounds of the Formula IV. The compounds of the Formula IV are further reacted with bromine, n-bromosuccinimide, NaOCl, or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to provide the compounds of the Formula II'₁. The compounds of the Formula II'₁ are subjected to saponification using KOH in water/iPrOH or the like to give the compounds of Formula II'₂.

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Scheme E



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The preparation of Scheme E provides the preferred method of preparation for the Compound II'₂ defined above.

5 Generally, the compounds of the formula I above wherein X is NHSO_2R^3 , NR^6R^3 , NR^6OR^3 , $\text{NR}^6\text{CONR}^3\text{R}^4$, NR^6COR^5 , $\text{NR}^6\text{CO}_2\text{R}^3$, $\text{NR}^6\text{NHSO}_2\text{R}^3$, $\text{NR}^6\text{NHCO}_2\text{R}^3$, wherein R_1 , R_2 , R_{11} , R_{12} , R^3 , R^4 , R^5 , and R^6 are as defined above, are prepared by the method of Schemes A-E above.

10 Scheme A consists of treating a carboxylic acid of the general structure (II) with a coupling reagent in an inert solvent to produce an activated carboxylic acid derivative. The resulting activated carboxylic acid derivative is reacted with a variety of nitrogen nucleophiles to produce amides of the general
15 structures I', wherein X, R^1 , R^2 , R^3 , R^4 , R^5 , and R^6 are as defined above. Suitable coupling agents for this purpose include, for example, such reagents as thionyl chloride, acetic anhydride, oxalyl chloride/
DMF, carbonyldiimidazole, DCC, and diphenylphosphoryl
20 azide, preferably carbonyldiimidazole. By "activated carboxylic acid derivative" is meant an acid derivative which is capable of acylating an amine. Such acid derivatives include, for example, acid chlorides, acid bromides, anhydrides, and mixed
25 anhydrides. By "inert solvent" is meant a nonprotic solvent such as, for example, methylene chloride, chloroform, carbon tetrachloride, ethyl acetate, tetrahydrofuran, and dimethylformamide.

30 Compounds of the Formula IIIa in Scheme C may be further reacted to protect the carbonyl of the quinoxaline ring with either a methoxy or allyloxy functionality to provide a compound of Formula IVa. The acid IVa is converted to the acid chloride followed by treatment with ammonia to produce the
35 amide Va. Compounds of the Formula Va are further

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elaborated by treatment with an isocyanate, symmetrical anhydride or a symmetrical pyrocarbonate to generate derivatives of structural Formula VIa. Formula VIa is deprotected with trimethylsilyl iodide or a combination of trimethylsilyl chloride and sodium iodide if the protecting ether is a methoxy group. The allyloxy group is removed using Wilkinson's catalyst to afford compounds of Formula VIIa.

Overall the compounds prepared in the Schemes A-E may optionally be further treated by conventional methods to obtain compounds of the Formula I wherein Y is S.

Pharmaceutically acceptable salts of the compounds of Formula I are also included as a part of the present invention.

The base salts may be generated from compounds of Formula I by reaction of the latter with one equivalent of a suitable nontoxic, pharmaceutically acceptable base followed by evaporation of the solvent employed for the reaction and recrystallization of the salt, if required. The compounds of Formula I may be recovered from the base salt by reaction of the salt with an aqueous solution of a suitable acid such as hydrobromic, hydrochloric, or acetic acid.

Suitable bases for forming base salts of the compounds of this invention include amines such as triethylamine or dibutylamine, or alkali metal bases and alkaline earth metal bases. Preferred alkali metal hydroxides and alkaline earth metal hydroxides as salt formers are the hydroxides of lithium, sodium, potassium, magnesium, or calcium. The class of bases suitable for the formation of nontoxic, pharmaceutically acceptable salts is well known to practitioners of the pharmaceutical formulation arts.

See, for exampl , Stephen N. Berge, et al, J. Pharm.
Sci. 1977;66:1-19.

Suitable acids for forming acid salts of the compounds of this invention containing a basic group include, but are not necessarily limited to acetic, benzoic, benzenesulfonic, tartaric, hydrobromic, hydrochloric, citric, fumaric, gluconic, glucuronic, glutamic, lactic, malic, maleic, methanesulfonic, pamoic, salicylic, stearic, succinic, sulfuric, and tartaric acids. The acid addition salts are formed by procedures well known in the art.

Further, the compounds of this invention may exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Starting materials for the processes described above are known or can be prepared by known processes.

The products of the reactions described herein are isolated by conventional means such as extraction, crystallization, distillation, chromatography, and the like.

PHARMACEUTICAL COMPOSITIONS

The compounds of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention,

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pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

10 In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

15 In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

20 The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

30 For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The

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molten homogeneous mixture is then poured into convenient sized molds, allowed to cool, and thereby to solidify.

5 Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

10 Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents, as desired.

15 Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

20 Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in
25 addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

30 The pharmaceutical preparation is preferably in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as
35 packeted tablets, capsules, and powders in vials or

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ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

5 The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg preferably 10 mg to 100 mg according to the particular application and the potency of the active component. The composition can, if desired, also
10 contain other compatible therapeutic agents.

METHOD OF TREATING

15 The compounds of this invention are extremely useful in the treatment of central nervous system disorders related to their biological activity. The compounds of this invention may accordingly be administered to a subject, including a human, in need of treatment, alleviation, or elimination of an
20 indication associated with the biological activity of the compounds. This includes especially excitatory amino acid dependent psychosis, excitatory amino acid dependent anorexia, excitatory amino acid dependent ischemia, excitatory amino acid dependent convulsions,
25 and excitatory amino acid dependent migraine. Suitable dosage ranges are 0.1 to 1000 mg daily, 10 to 400 mg daily, and especially 30 to 100 mg daily, dependent as usual upon the exact mode of administration, form in which administered, the
30 indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and further, the preference and experience of the physician or veterinarian in charge.

35 The following nonlimiting examples illustrate the present invention.

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General Preparation 1Preparation of Selected Acylsulphonamides

Solution A: 14.1 g, 0.087 mole
carbonyldiimidazole is dissolved in 250 mL dry DMF.
5 To this is added 0.029 mole of a suitably substituted
2-oxo-quinoxoline-3-carboxylate. This solution is
heated at 80°C for 2 hours under nitrogen, then dry
DMF to make 300 mL is added and the solution cooled to
25°C.

10 Solution B: To a suspension of 0.38 g,
0.0116 mole sodium hydride in 30 mL dry DMF is added
in one portion 0.0116 mole of the selected
sulphonamide. This is stirred at 25°C for 2 hours.

To Solution B is added 60 mL of Solution A at
15 once. A solid is formed at this point. In the cases
where the solid rapidly went into solution the
reaction is stirred at 25°C for 1 to 5 days. When a
solid remained after the mixing of the solutions, the
reaction is refluxed for 1 to 8 hours to go to
20 completion.

In either case, the reaction is worked up by
pouring into a mixture of 300 g each of ice and
concentrated HCl. The precipitated solid is washed
with water. The crude product is dissolved in hot DMF
25 and precipitated with the addition of water. After
cooling the solid is filtered, washed with cold DMF,
water, heptane, then dried for 24 hours at 140°C under
vacuum to yield the product as a yellow powder. In
some cases acetonitrile, diethyl ether, or methanol is
30 substituted for DMF as the washing solvent.

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General Preparation 2Preparation of 3,4-dihydro-N-alkoxy-3-oxo-2-quinoxaline carboxamides

5 Solution B: To a suspension of 0.38 g, 0.0116 mole sodium hydride in 30 mL anhydrous DMF is added in one portion 0.0116 mole of the selected O-alkylhydroxylamine hydrochloride or O-alkylarylhydroxylamine hydrochloride. This is stirred at 25°C for 1 hour.

10 To Solution B is added 60 mL of Solution A as described for Method A. The reaction is stirred at 25°C for 1 to 5 days. The reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% NaHCO₃, 50 mL water, 50 mL
15 acetonitrile, and 50 mL diethylether. The product is dried at 140°C under vacuum. In some cases the product is recrystallized from DMF/water or is triturated by washing with hot acetonitrile or
20 ethanol.

General Preparation 3Preparation of 3,4-dihydro-N-alkyl-3-oxo-2-quinoxaline carboxamides

25 Solution B: To a suspension of 0.38 g, 0.0116 mole sodium hydride in 20 mL anhydrous DMF is added in one portion 0.116 mole of the selected amine hydrochloride or alternatively the free base of the amine may be employed directly without the use of sodium hydride.

30 To Solution B is added 60 mL of Solution A as described for Method A. The reaction is stirred at 25°C for 1 to 5 days or stirred at 25°C for 18 hours and then heated to 80°C for 1 to 4 hours. The
35 reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% NaHCO₃,

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50 mL water, 50 mL acetonitrile, and 50 mL diethylether. The product is dried at 140°C under vacuum. In some cases the product is recrystallized from DMF/water or is triturated by washing with hot acetonitrile or ethanol.

General Preparation 4

Preparation of 3,4-dihydro-3-oxo-N-[(alkyl)amino]-carbonyl]-2-quinoxalinecarboxamides

10 To 60 mL of Solution A in Method A is added 1.49 g, 0.023 mol of sodium cyanate. The reaction is stirred at 25°C for 18 hours. The solvent is removed in vacuo at 60°C. Chloroform is added and the crude beige solid was filtered. The solid is slurried in 15 140 mL of anhydrous DMF and at least 0.046 mole of an alkyl or alkylaryl amine is added and the reaction was heated to 60°C for 18 hours. The reaction is poured into a mixture of 300 g each of ice and 3N HCl. The solid is washed with 50 mL 5% NaHCO₃, 50 mL water, 20 50 mL acetonitrile, and 50 mL diethylether. The product is purified on a silica gel column eluted initially with methylene chloride followed by methanol/methylene chloride up to 30% methanol. The chromatographed product is washed with hot 25 acetonitrile and filtered. The product is dried at 140°C under vacuum.

General Preparation 5

Preparation of 3,4-dihydro-3-[(alkoxy)carbonyl]-2-quinoxaline carboxamides

30 To 60 mL of Solution A is described in Method A is added 1.49 g, 0.023 mol of sodium cyanate. The reaction is stirred at 25°C for 18 hours. The solvent is removed in vacuo at 60°C. Chloroform is added and the crude beige solid was filtered. The solid is 35

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slurried in 140 mL of anhydrous DMF and at last
0.046 mole of an alcohol is added and the reaction is
heated to 60°C for 18 hours. The reaction is poured
into a mixture of 300 g each of ice and 3N HCl. The
5 solid is washed with 50 mL 5% NaHCO₃, 50 mL water,
50 mL acetonitrile, and 50 mL diethylether. The
product is purified on a silica gel column eluted
initially with methylene chloride followed by
methanol/methylene chloride up to 30% methanol. The
10 chromatographed product is washed with hot
acetonitrile and filtered. The product is dried at
140°C under vacuum.

15

EXAMPLE 1

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenyl)sulfonyl]-2-
quinoxalinecarboxamide

A solution containing benzenesulphonamide
(0.91 g, 5.8 mmol) and sodium hydride (0.24 g,
20 5.79 mmol) in dry DMF (10 mL) was heated to 60°C for
2 hours and cooled. A solution containing 3.9 mmol of
the reagent prepared as described in General
Preparation 1, Solution A was added to the
benzenesulfonamide mixture. The reaction was stirred
25 at 25°C for 18 hours, poured onto ice/HCl and the
precipitate was collected and dried to produce the
amide as a yellow solid (0.7 g, 90% yield); mp 325-
330°C.

Elemental analysis calculated for C₁₃H₁₄Cl₂N₄O₂:
30 C, 45.24; H, 2.28; N, 10.55; Cl, 17.80;
S, 8.05.
Found: C, 44.90; H, 1.94; N, 10.46; Cl, 17.90;
S, 8.24.

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EXAMPLE 2

6,7-Dichloro-N-[2-(dimethylamino)ethyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide

5 To a solution containing N,N'-dimethylethylenediamine (1.02 g, 11.6 mol) was in dry DMF (20 mL) was added a solution containing 5.8 mmol of the reagent prepared as described in General Preparation 1, Solution A. A yellow precipitate formed within 10 5 minutes and the reaction was stirred an additional 16 hours at 25°C. The reaction was poured onto ice and the precipitate was collected and dried to produce the amide as a yellow solid (1.38 g, 72% yield); m.p. 272-274°C.

Elemental analysis calculated for $C_{13}H_{14}Cl_2N_4O_2$:

15 C, 47.41; H, 4.20; N, 17.10.

Found: C, 47.43; H, 4.29; N, 17.02.

EXAMPLE 3

20 6,7-Dichloro-3,4-dihydro-3-oxo-N-(phenylmethoxy)-2-quinoxalinecarboxamide

Sodium hydride (2.49 g, 15.6 mmol) was suspended in anhydrous DMF (20 mL) and O-benzylhydroxyamine hydrochloride (2.49 g, 15.6 mmol) was added in one batch. The reaction was stirred for 1 hour and a 25 solution containing 7.7 mmol of the reagent prepared as described in General Preparation 1, Solution A was added. The reaction was stirred at 25°C for 4 days. The reaction was poured onto ice containing 6 N HCl and a yellow solid precipitated. The solid was 30 filtered and washed with water followed by hot acetonitrile to produce the hydroxamate (2.23 g, 79% yield); m.p. 279-280°C.

Elemental analysis calculated for $C_{16}H_{11}Cl_2N_3O_3$:

C, 52.77; H, 3.04; N, 11.54.

35 Found: C, 52.51; H, 2.97; N, 11.73.

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EXAMPLE 4

N-(Aminocarbonyl)-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide

5 4,5-Dichloro-1,2-phenylenediamine (8.0 g, 45.2 mmol) was dissolved in ethanol (300 mL) and water (30 mL). Alloxan monohydrate (7.24 g, 45.2 mmol) was dissolved in ethanol/water (30 mL:70 mL) and added dropwise to the diamine solution. The reaction was stirred for 20 hours and the precipitate was collected by filtration. This crude product was slurried in hot DMF (steam bath) and filtered. The solid was washed with water, acetonitrile, and diethylether to produce the title compound as a yellow solid (10.5 g, 77% yield); m.p. >300°C.

10

15 Elemental analysis calculated for $C_{10}H_6Cl_2N_4O_3$:
C, 39.89; H, 2.01; N, 18.61; Cl, 23.55.
Found: C, 39.75; H, 1.87; N, 18.52; Cl, 23.64.

EXAMPLE 5

20 6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenylmethyl)-amino]carbonyl]-2-quinoxalinecarboxamide

Sodium cyanate (1.0 g, 15.3 mmol) was added to a solution containing 3.35 mmol of the reagent prepared as described in General Preparation 1, Solution A.

25 The Reaction was stirred at 25°C for 18 hours. The solvent was removed in vacuo at 60°C and the solid

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liquor was further acidified to pH 2 and the yellow solid was filtered to produce a crude product (0.70 g) containing the title compound as the major component. This second solid was crystallized from DMF/water to afford the product as an off-white solid (0.67 g, 44% yield); m.p. 292-295°C.

Elemental analysis calculated for $C_{17}H_{12}Cl_2N_4O_3$:

C, 52.19; H, 3.09; N, 14.32; Cl, 18.12.

Found: C, 52.12; H, 3.27; N, 14.14; Cl, 18.03.

10

EXAMPLE 6

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenylamino)-carbonyl]-2-quinoxalinecarboxamide

Step 1

15 Ethyl-3,6,7-trichloro-2-quinoxalinecarboxylate

Ethyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylate (36.0 g, 0.125 mol) was suspended in toluene (500 mL) and DMF (12.5 mL) and thionyl chloride (12.5 mL, 0.17 mol) were added. The reaction was heated to reflux for 2 hours and the solution turned a deep purple. The reaction was cooled and the toluene was removed under reduced pressure. The crude material was chromatographed on a silica gel plug eluted with methylene chloride. The title compound was isolated as a pink solid (35.5 g, 93% yield). An analytical sample was prepared by recrystallization from hexane; m.p. 102-104°C. Elemental analysis calculated for $C_{11}H_7Cl_3N_2O_2$:

C, 43.24; H, 2.31; N, 9.17.

30

Found: C, 43.28; H, 2.23; N, 8.89.

Step 2

6,7-Dichloro-3-methoxy-2-quinoxalinecarboxylate

35 Sodium metal was added in small pieces to anhydrous MeOH (1500 mL) and the resulting sodium

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methoxide solution was cooled to 25°C. Ethyl-3,6,7-trichloro-2-quinoxalinecarboxylate (36.4 g, 0.119 mol) was added and the reaction was stirred for 18 hours. Water (500 mL) was added and the reaction was stirred for 3 hours at 25°C. The solvent was concentrated under reduced pressure to one-third of its original volume and the slurry was acidified to pH 2 with 25% hydrochloric acid. The mixture was stirred 30 minutes and the solid was filtered to yield the acid as a gray solid (30.8 g, 95% yield); m.p. 181-182°C.

Elemental analysis calculated for $C_{10}H_6Cl_2N_2O_3$:

C, 43.98; H, 2.21; N, 10.26.

Found: C, 43.92; H, 2.02; N, 10.24.

Step 3

6,7-Dichloro-3-methoxy-2-quinoxalinecarboxamide

6,7-Dichloro-3-methoxy-2-quinoxalinecarboxylate (16.38 g, 0.06 mol) was suspended in methylene chloride and oxalyl chloride (6.24 mL, 0.072 mol) and DMF (2 drops) was added. The reaction was stirred for 18 hours and the methylene chloride was removed under reduced pressure. The crude acid chloride was dissolved in anhydrous THF (500 mL) and ammonia gas was bubbled through the reaction for 1 hour. The reaction was then stirred for 18 hours at 25°C. The reaction was poured into water and the precipitate was collected by filtration to afford the amide as an off-white solid (14.41 g, 88% yield); m.p. 237-241°C.

Elemental analysis calculated for $C_{10}H_7Cl_2N_3O_2$:

C, 44.14; H, 2.59; N, 15.44.

Found: C, 44.07; H, 2.60; N, 15.33.

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Step 4

6,7-Dichloro-3-methoxy-N-[(phenylamino)carbonyl]-2-quinoxalinecarboxamide

5 6,7-Dichloro-3-methoxy-2-quinoxalinecarboxamide
(1.75 g, 0.0064 mol) was dissolved in toluene (500 mL)
and phenyl isocyanate (1.19 g, 0.01 mol) was added.
The reaction was refluxed for 24 hours and the toluene
layer was extracted with water, dried (MgSO_4),
filtered, and concentrated. The crude product was
10 chromatographed on silica gel eluted with $\text{CH}_2\text{Cl}_2/\text{MeOH}$
(95:5) to produce the acyl urea (1.44 g, 58% yield).
A sample was recrystallized from $\text{CH}_2\text{Cl}_2/\text{THF}$ to afford
an analytical sample.

Elemental analysis calculated for $\text{C}_{17}\text{H}_{12}\text{Cl}_2\text{N}_4\text{O}_3$:

15 C, 52.19; H, 3.09; N, 14.32.

Found: C, 52.10; H, 2.79; N, 14.16.

Step 5

20 6,7-Dichloro-3,4-dihydro-3-oxo-N-[(phenylamino)-
carbonyl]-2-quinoxalinecarboxamide

 6,7-Dichloro-3-methoxy-N-[(phenylamino)carbonyl]-
2-quinoxalinecarboxamide (1.25 g, 0.0032 mol) was
dissolved in methylene chloride (200 mL) and
trimethylsilyl iodide was added. The reaction was
25 stirred at 25°C for 18 hours. The reaction was poured
into 5% sodium bisulfite and stirred for 10 minutes.
The two layers were filtered to produce a crude solid.
The solid was dissolved in a minimum of DMF, stirred
over charcoal and filtered through a Celite pad. The
30 bright yellow solution was diluted with EtOH so that
the composition of the solution was approximately
EtOH/DMF (2:1). Water was added to the point of
cloudiness, the solution was cooled to 5°C and
filtered to produce the title compound as a yellow
35 solid (0.21 g, 17% yield); m.p. >300°C.

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Elemental analysis calculated for $C_{16}H_{10}Cl_2N_4O_3$:

C, 50.95; H, 2.67; N, 14.85.

Found: C, 50.73; H, 2.56; N, 14.83.

5

EXAMPLE 7

N-acetyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide

Step 1

10 6,7-Dichloro-3-(2-propenyloxy)-2-quinolinecarboxylic acid

Sodium metal (2.8 g, 0.122 mol) was added in small pieces to allyl alcohol (150 mL) over a 20-minute period. The allyloxy solution was cooled to 25°C and ethyl-3,6,7-trichloro-2-quinoxaline-carboxylate was added in one batch. The solid dissolved in solution briefly and a precipitate then formed. The reaction was stirred at 25°C for 18 hours and water (60 mL) was added and the reaction was stirred for an additional 4 hours. The allyl alcohol was removed under reduced pressure and water (100 mL) was added. The reaction was acidified to pH 2 with 6N hydrochloric acid. A precipitate formed and was filtered and washed with water to afford the title compound as a pale purple solid (6.58 g, 85% yield); m.p. 160-161°C.

Elemental analysis calculated for $C_{12}H_8Cl_2N_2O_3 \cdot 0.15H_2O$:

C, 47.76; H, 2.77; N, 2.98.

Found: C, 45.57; H, 2.77; N, 9.11.

30

Step 2

6,7-Dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide

35 6,7-Dichloro-3-[(1-propyl-2-ene)oxy]-2-quinoxalinecarboxylate (5.0 g, 0.0167 mol) was suspended in methylen chloride and oxalyl chl ride

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(1.75 mL, 0.02 mol) and DMF (2 drops) was added. The reaction was stirred for 4 hours and the methylene chloride was removed under reduced pressure. The crude acid chloride was dissolved in anhydrous THF (150 mL) and ammonia gas was bubbled through the reaction for 30 minutes. The reaction was then stirred for 18 hours at 25°C. The reaction was poured into water and the precipitate was collected by filtration to afford the amide as an off-white solid (4.57 g, 95% yield); m.p. 185-186°C.

Elemental analysis calculated for $C_{12}H_9Cl_2N_3O_2$:

C, 52.96; H, 4.44; N, 12.35.

Found: C, 51.53; H, 4.26; N, 12.04.

Step 3

Ethyl [[6,7-dichloro-3-(2-propenyloxy)-2-quinoxalinyll]carbonyl]carbamate

Dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide (0.5 g, 1.68 mmol) and diethyl-pyrocarbonate (20 mL) were heated at 140°C for 18 hours. The carbonate was removed under reduced pressure and the crude product was chromatographed on a silica gel column eluted with methylene chloride. The product eluted as a clear oil which solidified upon standing (0.32 g, 51% yield).

Step 4

Ethyl [[6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinyll]carbonyl]carbamate

6,7-Dichloro-3-[(1-propyl-2-ene)oxy]-N-(ethoxycarbonyl)-2-quinoxalinecarboxamide (0.32 g, 0.97 mmol) was dissolved in THF (18 mL) and water (2 mL) and tris(triphenylphosphine)rhodium chloride (30 mg). The reaction was refluxed for 30 minutes, cooled, and filtered through a C lite pad. The THF was removed under reduced pressure and the crude product was

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r crystallized from ethyl acetate to afford the title compound as a yell w solid (80 mg).

EXAMPLE 8

5 N-acetyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide

Step 1

N-acetyl-6,7-dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide

10 6,7-Dichloro-3-(2-propenyloxy)-2-quinoxaline-carboxamide (1.2 g, 0.004 mol) was suspended in acetic anhydride and heated to reflux for 18 hours. The reaction was cooled and the acetic anhydride was removed under reduced pressure at 60°C. The crude
15 solid was recrystallized from toluene to yield the imide as a beige solid (0.58 g, 43% yield).

Elemental analysis calculated for $C_{14}H_{10}Cl_2N_3O_3$:

C, 49.58; H, 2.97; N, 12.39.

Found: C, 49.32; H, 3.19; N, 12.29.

20

Step 2

N-acetyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide

25 N-acetyl-6,7-dichloro-3-(2-propenyloxy)-2-quinoxalinecarboxamide (0.50 g, 1.47 mmol) was dissolved in EtOH (18 mL) and water (2 mL) and tris(triphenylphosphine)rhodium chloride (50 mg). The reaction was refluxed for 30 minutes and a yellow solid precipitated out and filtered from the reaction
30 while it was hot. The solid was crystallized from DMF/water to produce the title compound as a bright yellow solid (0.22 g, 39% yield); m.p. 297-300°C (dec).

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Elemental analysis calculated for $C_{11}H_7Cl_2N_3O_3$:

C, 44.03; H, 2.35; N, 14.00.

Found: C, 43.76; H, 2.32; N, 13.85.

5

EXAMPLE 9

6,7-Dichloro-3,4-dihydro-3-oxo-2-(methoxycarbonyl)-
hydrazide-2-quinoxalinecarboxylic acid

To a solution of methylcarbazate (3.5 g, 38.6 mmol) in dry DMF (50 mL) is added a solution
10 containing 7.72 mol of the reagent prepared as described in General Preparation 1, Solution A. The reaction is stirred at 25°C for 4 days and poured into water (500 mL). The solution is made acidic with 6N HCl to pH 2. The precipitate is collected and
15 taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected by filtration and is washed with acetonitrile followed by diethylether to afford the
20 title compound (2.56 g, 100% yield); m.p. 333-340°C (decomposes).

Elemental analysis calculated for $C_{11}H_8N_4O_4Cl_2$:

C, 39.9; H, 2.44; N, 16.92; Cl, 21.41.

Found: C, 39.52; H, 2.29; N, 16.86; Cl, 21.94.

25

EXAMPLE 10

6,7-Dichloro-3,4-dihydro-3-oxo-2-(phenylsulfonyl)-
hydrazide-2-quinoxalinecarboxylic acid

Solution B: To a suspension of sodium hydride
30 (1.5 g, 38.6 mmol) (60% dispersion in mineral oil) in dry DMF (20 mL) is added benzenesulfonylhydrazide (6.65 g, 38.6 mmol). The reaction is stirred at 25°C for 1 hour and a solution containing 7.72 mmol of the reagent prepared as described in General
35 Preparation 1, Solution A is added to Solution B.

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This solution is stirred at 90°C for 24 hours and then is poured into water (500 mL). The solution is made acidic with 6N HCl to pH 2. The solid is collected and recrystallized twice from hot DMF/water, washed
5 with acetonitrile, followed by diethylether, and then dried at 137°C under vacuum to give the title compound (1.44 g, 45% yield) as a yellow solid; m.p. 283°C.

Elemental analysis calculated for $C_{15}H_{10}N_4O_4Cl_2S$:

C, 43.6; H, 2.44; N, 13.56; Cl, 17.16.

10 Found: C, 43.23; H, 2.26; N, 13.80; Cl, 17.69.

EXAMPLE 11

N-Benzoyl-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide

15 Solution B: To a suspension of sodium hydride (0.93 g, 23.2 mmol) (60% dispersion in mineral oil) in dry DMF (20 mL) is added benzamide (2.81 g, 23.2 mmol). The solution is stirred at 25°C for 1 hour. A solution containing 7.72 mmol of the
20 reagent prepared as described in General Preparation 1, Solution A is added to Solution B. The reaction is stirred at 25°C for 24 hours and the solution is poured into water (500 mL). The solution is made acidic with 6N HCl to pH 2. The solid is
25 collected and taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected, washed with acetonitrile followed by diethylether to give the
30 title compound (1.09 g, 39% yield) as a yellow solid; m.p. 302°C (decomposes).

Elemental analysis calculated for $C_{16}H_9N_3O_3Cl_2$:

C, 53.06; H, 2.5; N, 11.6; Cl, 19.58.

Found: C, 52.65; H, 2.28; N, 11.79; Cl, 19.78.

35

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EXAMPLE 12

6,7-Dichloro-3-hydroxy-N-(1-piperidinylcarbonyl)-2-quinoxalinecarboxamide

Solution B: To a suspension of sodium hydride
5 (0.93 g, 23.2 mmol) (60% dispersion in mineral oil) in
dry DMF (20 mL) is added 1-piperidinecarboxamide
(2.97 g, 23.2 mmol). The solution is stirred at 60°C
for 0.5 hours. A solution containing 0.00772 mol of
the reagent prepared as described in General
10 Preparation 1, Solution A is added to Solution B.
This is stirred at 60°C for 3 days. The solution is
poured into water (500 mL) and the solution is made
acidic with 6N HCl to pH 2. The solid is collected
and taken up in hot DMF. The DMF solution is treated
15 with charcoal and filtered. The solution is cooled
and diluted with an equal volume of water. The yellow
solid is collected, washed with acetonitrile followed
by diethylether to give the title compound (0.95 g,
33% yield) as a yellow solid; m.p. 277-278°C.
20 Elemental analysis calculated for C₁₂H₁₀N₂O₂Cl₂:

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acidic with 6N HCl to pH 2. The solid is collected and taken up in hot DMF. The DMF solution is treated with charcoal and filtered. The solution is cooled and diluted with an equal volume of water. The yellow solid is collected, washed with acetonitrile followed by diethylether to afford the title compound (1.5 g, 59% yield) as a yellow solid; m.p. 289-90°C.

Elemental analysis calculated for $C_{12}H_{10}N_4O_3Cl_2$:

C, 43.79; H, 3.06; N, 17.02; Cl, 21.54.

Found: C, 43.76; H, 3.03; N, 16.95; Cl, 21.60.

Likewise, in a manner analogous to the procedures of General Preparations 1-3, but using appropriate corresponding starting materials the following compounds were prepared.

EXAMPLE 14

α -[[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxaliny)]-carbonyl]amino-(\pm)-benzeneacetic acid; 9.8% yield, m.p. 244-252°C (dec.)

Calcd.: C, 52.06; H, 2.83; N, 10.71.

Found: C, 51.98; H, 2.89; N, 10.85.

EXAMPLE 15

6,7-Dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxalinecarboxamide; 32% yield; m.p. >355°C.

Calcd: C, 35.73; H, 2.10; N, 12.50.

Found: C, 35.74; H, 2.02; N, 12.27.

EXAMPLE 16

6,7-Dichloro-3,4-dihydro-N-hydroxy-3-oxo-2-quinoxalinecarboxamide; 44% yield; m.p. >300°C.

Calcd: C, 39.44; H, 1.84; N, 15.33.

Found: C, 39.22; H, 1.59; N, 14.95.

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EXAMPLE 17

N-(Butylsulfonyl)-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; m.p. >295°C.

Calcd: C, 41.28; H, 3.46; N, 11.11.

5 Found: C, 41.22; H, 3.22; N, 11.22.

EXAMPLE 18

6,7-Dichloro-3,4-dihydro-N-methyl-3-oxo-2-quinoxalinecarboxamide; 95% yield; m.p. >300°C.

10 Calcd: C, 44.14; H, 2.59; N, 15.44.

Found: C, 43.83; H, 2.67; N, 15.10.

EXAMPLE 19

6,7-Dichloro-3,4-dihydro-N-methoxy-3-oxo-2-quinoxalinecarboxamide; 67% yield; m.p. 298-300°C.

15 Calcd: C, 41.69; H, 2.45; N, 14.59.

Found: C, 41.66; H, 2.37; N, 14.22.

EXAMPLE 20

6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 94% yield; m.p. >320°C.

20 Calcd: C, 41.89; H, 1.95; N, 16.28.

Found: C, 41.62; H, 1.63; N, 16.06.

EXAMPLE 21

6,7-Dichloro-3,4-dihydro-3-oxo-N-(phenylmethyl)-2-quinoxalinecarboxamide; 86% yield; m.p. >320°C.

25 Calcd: C, 55.19; H, 3.18; N, 12.07.

Found: C, 54.97; H, 3.18; N, 11.96.

30

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EXAMPLE 22

1-[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxaliny)-
carbonyl]-4-(phenylmethyl-piperazine
monohydrochloride; m.p. >290°C (dec).

5 Calcd: C, 52.94; H, 4.22; N, 12.35.

Found: C, 52.59; H, 4.40; N, 12.45.

EXAMPLE 23

10 [[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxaliny)-
carbonyl]amino acetic acid, 1,1-dimethylethyl ester;
74% yield; m.p. >300°C.

Calcd (with 0.25 H₂O):

C, 47.83; H, 4.15; N, 11.16; Cl, 18.82.

Found: C, 47.65; H, 4.05; N, 11.18; Cl, 18.84.

15

EXAMPLE 24

N-[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxaliny)-
carbonyl]glycine; 98% yield; m.p. 285-306°C (dec).

Calcd: C, 41.80; H, 2.23; N, 13.29.

20 Found: C, 41.52; H, 2.04; N, 13.14.

EXAMPLE 25

25 [[[(6,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxaliny)-
carbonyl]aminolacetic acid; 62% yield; m.p. 248-268°C
(dec).

Calcd: C, 39.78; H, 2.12; N, 12.65.

Found: C, 39.71; H, 2.17; N, 13.09.

EXAMPLE 26

30 6,7-Dichloro-3,4-dihydro-N-[(4-methylphenyl)sulfonyl]-
3-oxo-2-quinoxalinecarboxamide; 43% yield; m.p. 320°C.

Calcd: C, 46.62; H, 2.69; N, 10.19; Cl, 17.20;
S, 7.78.

Found: C, 46.47; H, 2.61; N, 10.08; Cl, 17.33;

35

S, 7.66.

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EXAMPLE 27

6,7-Dichloro-3,4-dihydro-N-[(2-chloro-5-nitrophenyl)-sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 81% yield;
m.p. 340°C.

5 Calcd: C, 37.72; H, 1.48; N, 11.73; Cl, 22.27;
S, 6.71.
Found: C, 38.10; H, 1.52; N, 11.66; Cl, 22.01;
S, 7.01.

EXAMPLE 28

10 6,7-Dichloro-N-[(4-chloro-2-nitrophenyl)sulfonyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 93% yield;
m.p. 330°C.

15 Calcd: C, 37.72; H, 1.48; N, 11.73; Cl, 22.27;
S, 6.71.
Found: C, 37.61; H, 1.28; N, 11.53; Cl, 22.27;
S, 7.19.

PREPARATION 1

20 3,4-Dihydro-7-nitro-3-oxo-2-quinoxalinecarboxylic acid
3-Hydroxy-2-quinoxaline carboxylic acid (10.0 g,
52.6 mmole) was dissolved in concentrated H₂SO₄
(150 mL), and cooled in an ice bath. Powdered
potassium nitrate (16.0 g, 178 mmole), was added in
25 portions with stirring, and the reaction was allowed
to warm overnight. In the morning the reaction was
poured onto 600 g ice and when the ice melted the
precipitate was filtered. The solid was dissolved in
boiling water (1600 mL), hot filtered, and then cooled
30 and the precipitate filtered to give (7.5 g, 64%) of
the title compound. Recrystallization from
ethanol/water afforded 3,4-dihydro-7-nitro-3-oxo-2-
quinoxalinecarboxylic acid as a yellow solid.

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Elemental analysis calculated for 2 mole H₂O:

C; 39.89; H, 3.34; N, 15.51.

Found: C, 39.89; H, 3.37; N, 15.30.

5 Preparations 2 and 3 are analogous to those of
U.S. Patent 4,264,600 beginning with corresponding
appropriate starting materials.

PREPARATION 2

10 Ethyl-6-nitro-3,4-dihydro-3-oxo-quinoxaline-2-
carboxylate; 52% yield; m.p. 229°C.

Calcd: C, 50.16; H, 3.48; N, 15.78.

Found: C, 50.20; H, 3.45; N, 15.96.

15 PREPARATION 3

6-Nitro-3,4-dihydro-3-oxo-quinoxaline-2-carboxylic
acid; 75% yield; m.p. 270°C.

Calcd: C, 45.97; H, 2.14; N, 17.87.

Found: C, 45.82; H, 2.10; N, 17.75.

20

EXAMPLE 29

6,7-Dichloro-3,4-dihydro-N-(2-thionylsulfonyl)-3-oxo-
2-quinoxalinecarboxamide; 22% yield; m.p. 320°C.

Calcd: C, 38.63; H, 1.25; N, 10.39; Cl, 17.54.

25

Found: C, 38.75; H, 1.58; N, 10.29; Cl, 17.71.

EXAMPLE 30

6,7-Dichloro-3,4-dihydro-N-[(4-methoxyphenyl)-
sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 45% yield;
30 m.p. 313°C.

Calcd: C, 44.87; H, 2.59; N, 9.81; Cl, 16.56;
S, 7.49.

Found: C, 44.75; H, 2.65; N, 9.74; Cl, 16.46;
S, 7.72.

35

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EXAMPLE 31

6,7-Dichloro-3,4-dihydro-N-[(4-bromophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 25% yield; m.p. 330°C.

Calcd: C, 37.76; H, 1.69; N, 8.81; Cl, 14.86;
Br, 16.75.

Found: C, 38.93; H, 1.90; N, 8.42; Cl, 14.76;
Br, 17.03.

EXAMPLE 32

6,7-Dichloro-3,4-dihydro-N-[(2-methylphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 21% yield; m.p. 322°C.

Calcd: C, 46.62; H, 2.69; N, 10.19; Cl, 17.20;
S, 7.78.

Found: C, 46.66; H, 2.63; N, 10.12; Cl, 17.28;
S, 7.72.

EXAMPLE 33

6,7-Dichloro-3,4-dihydro-N-[(4-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 12% yield; m.p. 335°C.

Calcd: C, 41.64; H, 1.86; N, 9.71.

Found: C, 41.41; H, 1.96; N, 9.62.

EXAMPLE 34

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[5-(2-pyridinyl)-2-thienyl]sulfonyl]-2-quinoxalinecarboxamide; 52% yield;
m.p. 325°C.

Calcd: C, 44.92; H, 2.09; N, 11.64.

Found: C, 45.49; H, 2.03; N, 11.21.

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EXAMPLE 35

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[3-(trifluoromethyl)phenyl]sulfonyl]-2-quinoxalinecarboxamide; 25% yield; m.p. 310-312°C.

5 Calcd: C, 41.22; H, 1.73; N, 9.01; Cl, 15.21;
F, 12.22; S, 6.89.
Found: C, 41.10; H, 1.43; N, 9.12; Cl, 15.55;
F, 18.82; S, 6.55.

10

EXAMPLE 36

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(4-fluorophenyl)sulfonyl]-2-quinoxalinecarboxamide; 33% yield; m.p. 313-315°C.

Calcd: C, 43.29; H, 1.94; N, 10.10; Cl, 17.04;
15 F, 4.56; S, 7.70.
Found: C, 43.07; H, 2.01; N, 9.97; Cl, 17.02;
F, 7.40; S, 7.70.

EXAMPLE 37

20 6,7-Dichloro-N-[(2,3-dihydro-(H-inden-5-yl)sulfonyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide; 22% yield; m.p. 320-322°C.

Calcd: C, 49.33; H, 2.99; N, 9.59; Cl, 16.18;
S, 7.32.
25 Found: C, 49.46; H, 2.94; N, 9.68; Cl, 16.95;
S, 7.31.

EXAMPLE 38

30 6,7-Dichloro-3,4-dihydro-N-[(3-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 64% yield; m.p. 320°C.

Calcd: C, 41.64; H, 1.86; N, 9.71; Cl, 24.58;
S, 7.41.
Found: C, 41.58; H, 1.87; N, 9.60; Cl, 24.90;
35 S, 6.99.

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EXAMPLE 39

6,7-Dichloro-3,4-dihydro-N-[(2-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide; 22% yield;

m.p. 317-318°C.

5 Calcd: C, 41.64; H, 1.86; N, 9.71; Cl, 24.58;
S, 7.41.
Found: C, 41.63; H, 1.17; N, 9.82; Cl, 24.29;
S, 7.91.

EXAMPLE 40

6,7-Dichloro-3,4-dihydro-N-(2-naphthalenylsulfonyl)-3-oxo-2-quinoxalinecarboxamide; 32% yield;

m.p. 306-308°C.

10 Calcd: C, 50.91; H, 2.47; N, 9.37; Cl, 15.82;
15 S, 7.15.
Found: C, 51.03; H, 2.11; N, 9.39; Cl, 15.86;
S, 7.10.

EXAMPLE 41

20 6,7-Dichloro-3,4-dihydro-3-oxo-N-[(3-nitrophenyl)sulfonyl]-2-quinoxalinecarboxamide; 55% yield;

m.p. 325-327°C.

Calcd: C, 40.65; H, 1.82; N, 12.64; Cl, 16.00;
S, 7.23.
25 Found: C, 40.42; H, 1.46; N, 12.55; Cl, 16.04;
S, 7.56.

EXAMPLE 42

30 6,7-Dichloro-3,4-dihydro-3-oxo-N-[(4-nitrophenyl)sulfonyl]-2-quinoxalinecarboxamide; 55% yield;

m.p. 316-319°C.

Calcd: C, 40.65; H, 1.82; N, 12.64; Cl, 16.00;
S, 7.23.
Found: C, 40.55; H, 1.66; N, 12.58; Cl, 16.40;
35 S, 7.10.

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EXAMPLE 43

6,7-Dichloro-3,4-dihydro-3-oxo-N-[(2-nitrophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 77% yield;
m.p. 313-317°C.

5 Calcd: C, 40.65; H, 1.82; N, 12.64; Cl, 16.00;
S, 7.23.
Found: C, 40.74; H, 1.85; N, 12.40; Cl, 16.64;
S, 6.81.

10

EXAMPLE 44

6,7-Dichloro-3,4-dihydro-3-oxo-N-[[2,4,6-tris(1-methylethyl)phenyl]sulfonyl]-2-quinoxalinecarboxamide;
12% yield; m.p. 289°C.

15 Calcd: C, 54.96; H, 5.19; N, 8.01; Cl, 13.52;
S, 6.11.
Found: C, 54.71; H, 5.04; N, 8.00; Cl, 13.21;
S, 5.99.

EXAMPLE 45

20 6,7-Dichloro-3,4-dihydro-3-oxo-N-[(2-fluorophenyl)-sulfonyl]-2-quinoxalinecarboxamide; 30% yield;
m.p. 312-314°C.

Calcd: C, 43.29; H, 1.94; N, 10.10; Cl, 17.04;
F, 4.56; S, 7.70.
25 Found: C, 43.09; H, 1.63; N, 10.04; Cl, 17.38;
F, 4.90; S, 7.53.

EXAMPLE 46

30 6,7-Dichloro-3,4-dihydro-3-oxo-N-[(pentamethylphenyl)-sulfonyl]-2-quinoxalinecarboxamide; 36% yield;
m.p. 270°C.

Calcd: C, 51.29; H, 4.09; N, 8.97; S, 6.85.
Found: C, 51.11; H, 3.81; N, 8.94; S, 6.95.

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EXAMPLE 47

N-[(1,2-Benzisoxazol-3-ylmethyl)sulfonyl]-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide;
56% yield; m.p. 283-285°C.

5 Calcd: C, 45.05; H, 2.22; N, 12.36; Cl, 15.64;
S, 7.07.

Found: C, 44.77; H, 2.25; N, 12.27; Cl, 16.04;
S, 6.92.

10 The following additional preparations of
compounds here are within procedures as set out in
U.S. Patent No. 4,264,600.

PREPARATION 4

15 Ethyl-6,7-dimethyl-3,4-dihydro-3-oxo-2-quinoxaline-
carboxylate

PREPARATION 5

20 6,7-Dimethyl-3,4-dihydro-3-oxo-2-quinoxaline-
carboxylate; 97% yield; m.p. 304-308°C.

Analysis for 2 mole H₂O:

Calcd: C, 59.22; H, 4.76; N, 12.56.

Found: C, 59.22; H, 4.41; N, 12.62.

PREPARATION 6

25 Ethyl-3,4-dihydro-3-oxo-benzo(g)-quinoxaline-2-
carboxylate; 79% yield; m.p. 205°C.

Calcd: C, 67.16; H, 4.51; N, 10.44.

Found: C, 67.35; H, 4.51; N, 10.68.

30

PREPARATION 7

Ethyl-5,8-dibromo-3,4-dihydro-3-oxo-quinoxaline-2-
carboxylate; 89% yield; m.p. 205°C.

Calcd: C, 35.14; H, 2.14; N, 7.45.

35 Found: C, 35.05; H, 1.94; N, 6.99.

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PREPARATION 8

5,8-Dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylic acid; 74% yield; m.p. 280-283°C.

Calcd: C, 31.07; H, 1.16; N, 8.05; Br, 45.93.

5 Found: C, 30.97; H, 1.15; N, 8.10; Br, 48.30.

PREPARATION 9

Ethyl-6,7-dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylate; 78% yield; m.p. 238°C.

10 Calcd: C, 35.14; H, 2.14; N, 7.45; Br, 42.50.

Found: C, 35.22; H, 2.09; N, 6.92; Br, 42.76.

PREPARATION 10

6,7-Dibromo-3,4-dihydro-3-oxo-quinoxaline-2-carboxylic acid; 82% yield; m.p. >300°C.

15

Calcd: C, 31.07; H, 1.16; N, 8.05.

Found: C, 31.18; H, 1.32; N, 8.32.

PREPARATION 11

Ethyl-6,7-dinitro-3,4-dihydro-3-oxo-quinoxaline-2-carboxylate; 36% yield; m.p. 220°C.

20

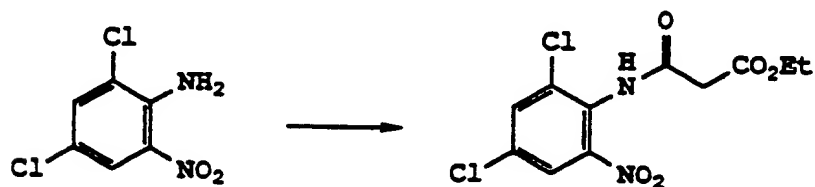
Calcd: C, 42.87; H, 2.62; N, 18.18.

Found: C, 42.54; H, 2.52; N, 17.78.

25

PREPARATION 1a

30



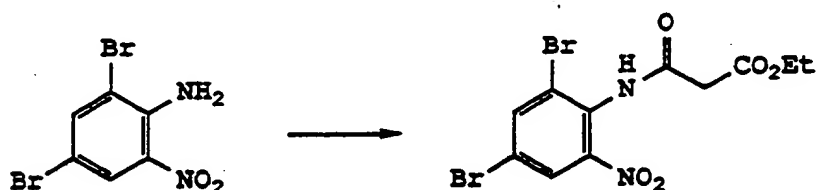
Ethyl 3-[(2,4-dichloro-6-nitrophenyl)amino]-3-oxopropanoate

35 A solution of 4,6-dichloro-2-nitroaniline (31.0 g, 0.15 m l) and chlor ethylmal nat (25.0 g,

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0.17 mol) in toluene (500 mL) was heated at reflux for 24 hours. The reaction mixture was cooled and concentrated. The residue was dissolved in hot ethanol, decolorized with charcoal, and filtered. The solid which formed on cooling was collected by suction filtration and dried to give the title compound as a yellow solid (13.6 g, 28%).

PREPARATION 2a

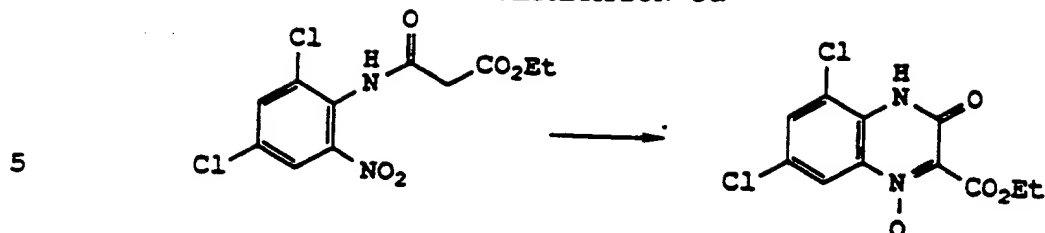


Ethyl 3-[(2,4-dibromo-6-nitrophenyl)amino]-3-oxopropanoate

A solution of 4,6-dibromo-2-nitroaniline (44.3 g, 0.15 mol) and chloroethylmalonate (25.0 g, 0.17 mol) in toluene (500 mL) was heated at reflux for 24 hours. The reaction mixture was cooled and the solid which formed was collected by suction filtration. The solid was suspended in diisopropyl ether, filtered, and dried under vacuum to give the title compound as a

-57-

PREPARATION 3a



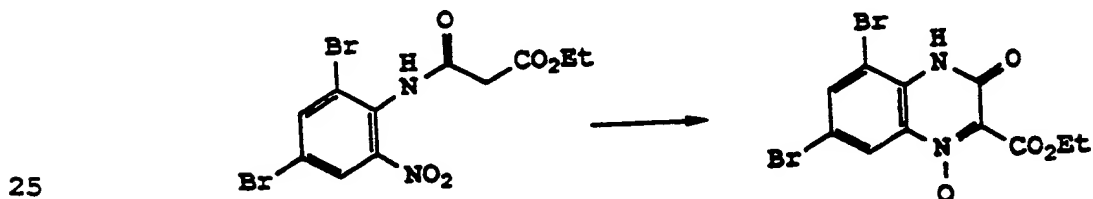
Ethyl 5,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-
carboxylate 1-oxide

10 Sodium (2.57 g, 0.112 mol) was dissolved in ethanol (500 mL) and the resulting solution was treated with the product from Preparation 1a (22.7 g, 71.0 mmol) in one portion and the resulting solution was heated to reflux for 45 minutes. The reaction mixture cooled to 0°C and treated with 1N HCl

15 (125 mL). The solid which formed was collected by suction filtration and crystallized from hot ethanol to give the title compound as a yellow solid (9.84 g, 46%).

20

PREPARATION 4a

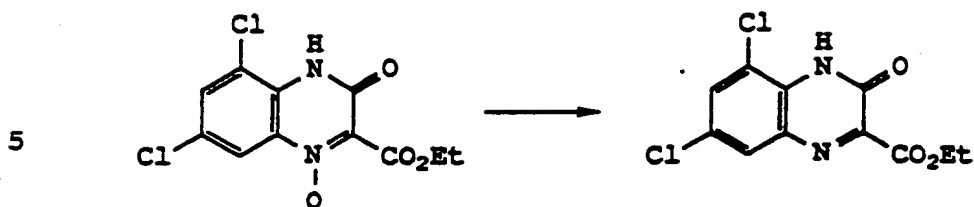


Ethyl 5,7-dibromo-3,4-dihydro-3-oxo-2-quinoxaline-
carboxylate 1-oxide

30 In a manner similar to that described in Preparation 3a, the product of Preparation 2a (30.0 g) was converted to the title compound as a yellow solid (13.3 g, 46%).

-58-

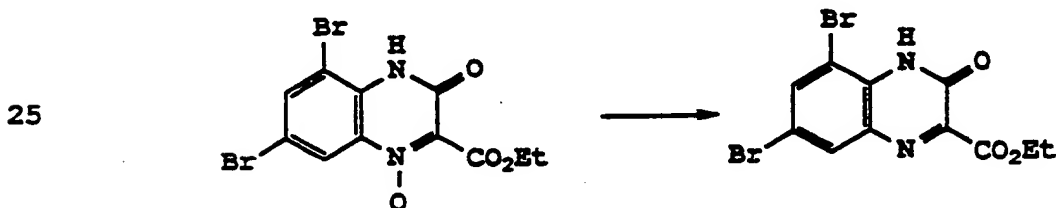
PREPARATION 5a



Ethyl 5,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-
carboxylate

10 A solution of the product from Preparation 3a (5.00 g, 17.3 mmol) and phosphorous trichloride (30 mL) in tetrahydrofuran (200 mL) was heated at reflux for 24 hours. The reaction was cooled and poured over ice. The resulting suspension was
15 extracted into CH_2Cl_2 . The organic phase was washed with water, dried (Na_2SO_4), and concentrated. The residue was suspended in EtOH, collected by suction filtration, and dried to give the title compound as a
20 yellow solid (1.67 g, 34%).

PREPARATION 6a

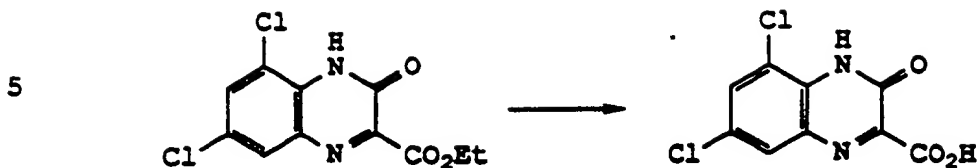


Ethyl 5,7-dibromo-3,4-dihydro-3-oxo-2-quinoxaline-
carboxylate

30 In a manner similar to that described in Preparation 5a, the product of Preparation 4a (13.4 g, 34.2 mmol) was converted to the title compound as a yellow solid (3.64 g, 28%).

-59-

PREPARATION 7a



10 5,7-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

A solution of the product from Preparation 5a (2.14 g, 8.26 mmol) and potassium hydroxide (2.08 g, 37.1 mmol) in 3:1 water/iPrOH (100 mL) was heated at reflux for 2 hours. The reaction mixture was cooled to room temperature and acidified to pH 1 with concentrated HCl. The solid which formed was collected by suction filtration and dried to give the title compound as a yellow solid (1.86 g, 87%), m.p. 196-198°C.

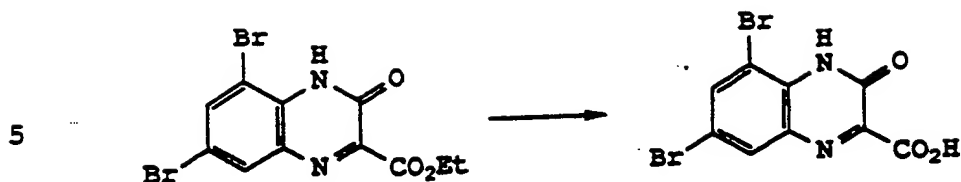
20 Elemental analysis calculated for $C_9H_4Cl_2N_2O_3$:

C, 41.73; H, 1.56; N, 10.81.

Found: C, 41.43; H, 1.33; N, 10.77.

-60-

PREPARATION 8a



10

5,7-Dibromo-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product of Preparation 6a (2.41 g, 6.41 mmol) was converted to the title compound as a yellow solid (2.41 g, 34%), m.p. 202-206°C.

Elemental analysis calculated for $C_9H_4Br_2N_2O_3$:

15 C, 31.07; H, 1.06; N, 8.05.

Found: C, 31.26; H, 1.01; N, 8.20

PREPARATION 9a



25

5,7-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product of Preparation 7a (0.50 g, 1.93 mmol) was converted to the title compound as a yellow solid (0.55 g, 71%), m.p. 286-290°C.

Elemental analysis calculated for $C_{15}H_9Cl_2N_3O_4S$:

30 C, 45.24; H, 2.28; N, 10.55; S, 8.05.

Found: C, 44.90; H, 2.16; N, 10.31; S, 7.74.

35

-61-

PREPARATION 10a



5,7-Dibromo-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinolinecarboxamide

10 A solution of the product from Preparation 8a (0.50 g, 1.44 mmol) in DMF (12 mL) was treated with carbonyl diimidazole (0.70 g) and the resulting solution was heated at 60°C for 4 hours. Concurrently a suspension of benzenesulfonamide (0.67 g, 4.26 mmol) and NaH (0.17 g, 4.57 mmol) in DMF (10 mL) was stirred

15 for 4 hours at room temperature. The two reaction mixtures were combined and the resulting solution was stirred at room temperature overnight. The reaction mixture was poured onto ice and 1N HCl. The solid

20 which formed was collected by suction filtration, washed with water, and dried under vacuum (P₂O₅) to give the title compound as a yellow solid (0.44 g, 63%), m.p. 290-293°C.

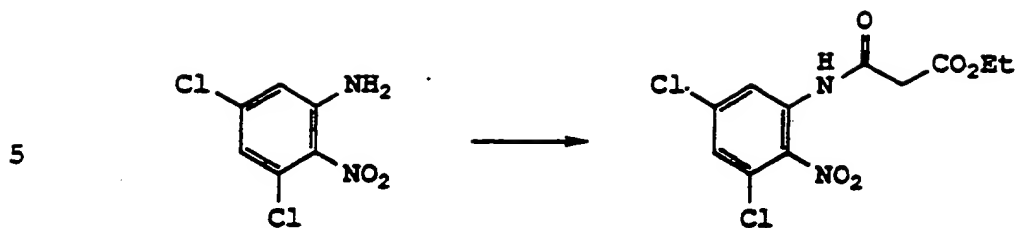
Elemental analysis calculated for C₁₅H₁₀Br₂N₃O₄S:

25 C, 36.98; H, 1.86; N, 8.63; S, 6.58.

Found: C, 36.80; H, 1.71; N, 8.43; S, 6.57.

-62-

PREPARATION 11a



Ethyl 3-[(3,5-dichloro-2-nitrophenyl)amino]-3-oxopropanoate

10 In a manner similar to that described in Preparation 1a, 3,5-dichloro-2-nitroaniline (47.5 g, 0.229 mol) was converted to the title compound as a yellow solid (51.7 g, 70%).

PREPARATION 12a

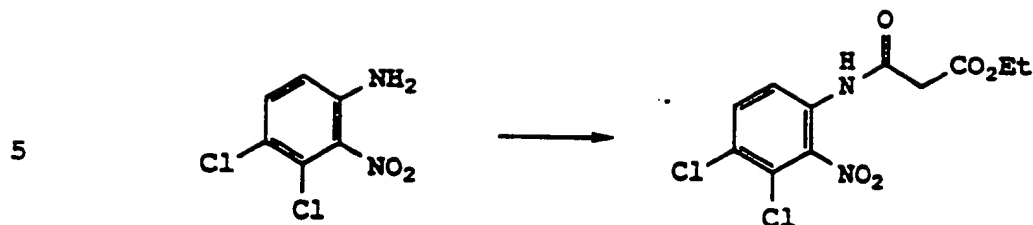


Ethyl 3-[(2,3-dichloro-6-nitrophenyl)amino]-3-oxopropanoate

25 In a manner similar to that described in Preparation 1a, 5,6-dichloro-2-nitroaniline is converted to the title compound.

-63-

PREPARATION 13a

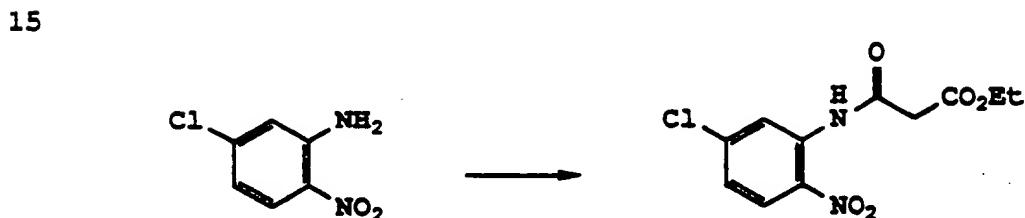


10

Ethyl 3-[(3,4-dichloro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 3,4-dichloro-2-nitroaniline is converted to the title compound.

PREPARATION 14a



20

Ethyl 3-[(5-chloro-2-nitrophenyl)amino]-3-oxopropanoate

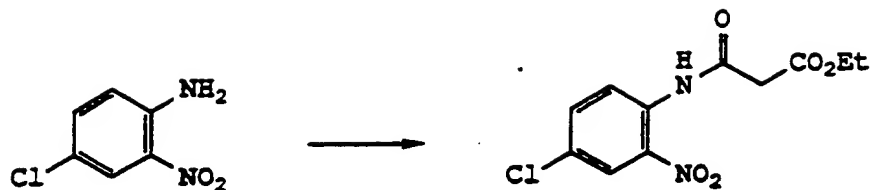
25

In a manner similar to that described in Preparation 1a, 5-chloro-2-nitroaniline (26.0 g, 0.15 mol) is converted to the title compound as a yellow solid (34.5 g, 80%).

-64-

PREPARATION 15a

5



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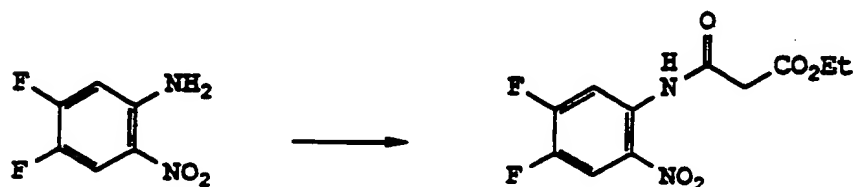
Ethyl 3-[(4-chloro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 4-chloro-2-nitroaniline (26.0 g, 0.15 mol) is converted to the title compound as a yellow solid (33.8 g, 78%).

15

PREPARATION 16a

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Ethyl 3-[(4,5-difluoro-2-nitrophenyl)amino]-3-oxopropanoate

In a manner similar to that described in Preparation 1a, 4,5-difluoro-2-nitroaniline (20.0 g, 0.115 mol) is converted to the title compound as a yellow solid.

-65-

PREPARATION 17a



Ethyl 3-[(4-fluoro-2-nitrophenyl)amino]-3-oxopropanoate

10 In a manner similar to that described in Preparation 1a, 4-fluoro-2-nitroaniline (21.6 g, 0.138 mol) is converted to the title compound as a yellow solid (19.4 g, 52%).

15

PREPARATION 18a

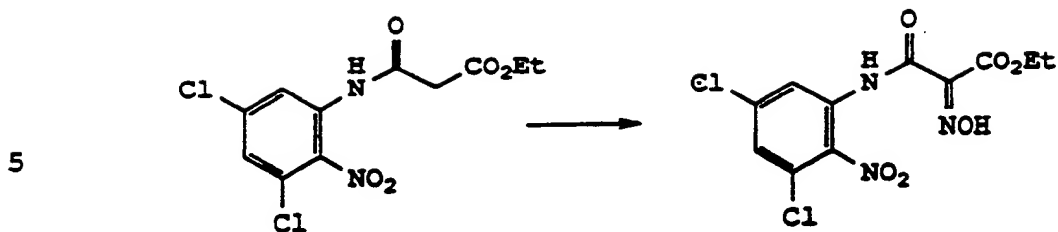


Ethyl 3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-3-oxopropanoate

25 In a manner similar to that described in Preparation 1a, 4-amino-3-nitrobenzotrifluoride (31.1 g, 0.151 mol) is converted to the title compound as a yellow solid (31.9 g, 66%).

-66-

PREPARATION 19a

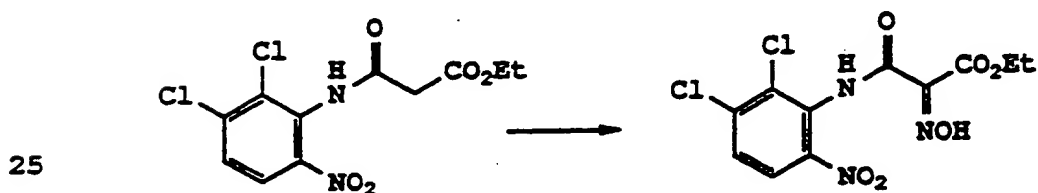


Ethyl 3-[(3,5-dichloro-2-nitrophenyl)amino]-2-
(hydroxyimino)-3-oxopropanoate

10 A solution of the product from Preparation 11a (7.00 g, 23.9 mmol) in 4:2:1 AcOH/THF/H₂O (210 mL) was treated with NaNO₂ (1.81 g, 26.3 mmol) in one portion and stirred at room temperature for 4 hours. Additional NaNO₂ (1.81 g, 26.3 mmol) was added and
15 stirring was continued overnight. The reaction was extracted into CH₂Cl₂, dried (MgSO₄), filtered, and concentrated to give the title compound as a yellow solid (4.33 g, 76%).

20

PREPARATION 20a

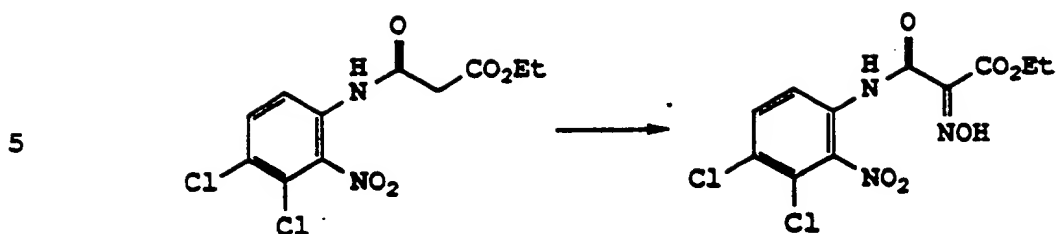


Ethyl 3-[(2,3-dichloro-2-nitrophenyl)amino]-2-
(hydroxyimino)-3-oxopropanoate

30 In a manner similar to that described in Preparation 19a, the product from Example 12a is converted to the title compound.

-67-

PREPARATION 21a

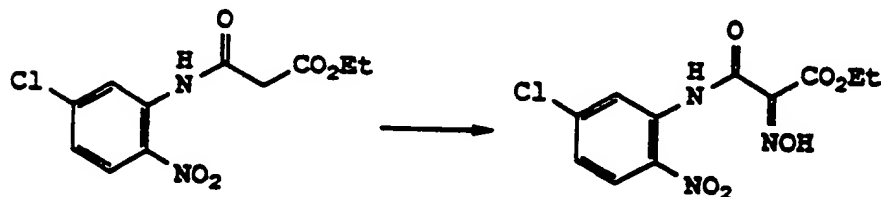


Ethyl 3-[(3,4-dichloro-2-nitrophenyl)amino]-2-
(hydroxyimino)-3-oxopropanoate

10 In a manner similar to that described in Preparation 19a, the product from Preparation 13a is converted to the title compound.

PREPARATION 22a

15



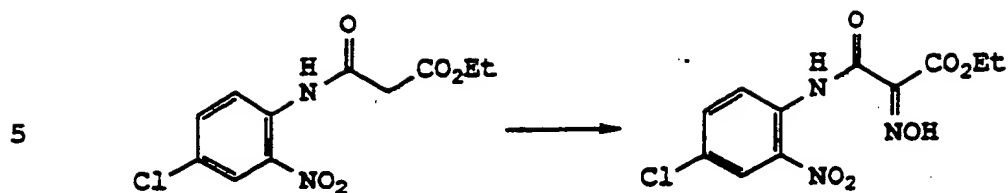
20

Ethyl 3-[(5-chloro-2-nitrophenyl)amino]-2-
(hydroxyimino)-3-oxopropanoate

25 In a manner similar to that described in Preparation 19a, the product from Preparation 14a (10.0 g, 36.7 mmol) is converted to the title compound as a yellow solid (9.24 g, 80%).

-68-

PREPARATION 23a

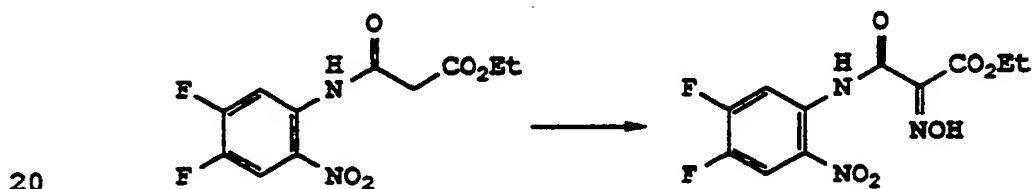


Ethyl 3-[(4-chloro-2-nitrophenyl)amino]-2-
(hydroxyimino)-3-oxopropanoate

10 In a manner similar to that described in Preparation 19a, the product from Preparation 15a (10.0 g, 36.7 mmol) is converted to the title compound as a yellow solid (9.83 g, 85%).

15

PREPARATION 24a

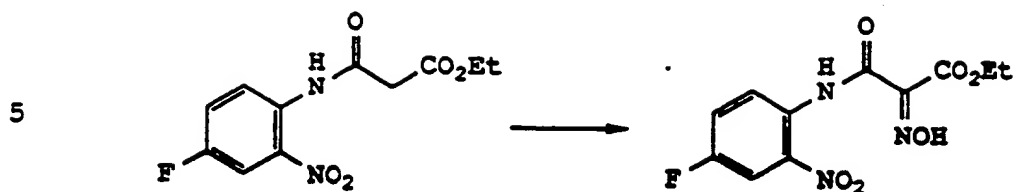


Ethyl 3-[(4,5-difluoro-2-nitrophenyl)amino]-2-
(hydroxyimino)-3-oxopropanoate

25 In a manner similar to that described in Preparation 19a, the product from Preparation 16a is converted to the title compound.

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PREPARATION 25a

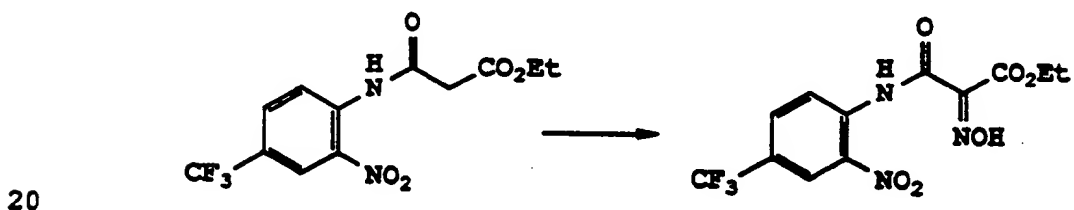


Ethyl 3-[(4-fluoro-2-nitrophenyl)amino]-2-(hydroxyimino)-3-oxopropanoate

10 In a manner similar to that described in Preparation 19a, the product from Preparation 17a is converted to the title compound.

PREPARATION 26a

15

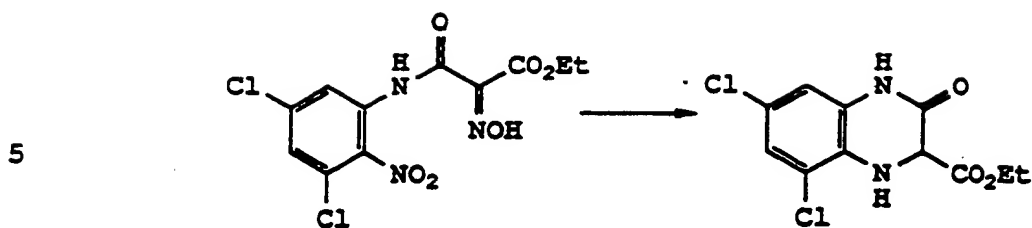


Ethyl 2-(hydroxyimino)-3-[[2-nitro-4-(trifluoromethyl)phenyl]amino]-3-oxopropanoate

25 In a manner similar to that described in Preparation 19a, the product from Preparation 18a (10.0 g, 31.2 mmol) is converted to the title compound as a yellow solid (9.49 g, 87%).

-70-

PREPARATION 27a



Ethyl 6,8-dichloro-1,2,3,4-tetrahydro-3-oxo-2-
quinoxalinecarboxylate

10 A solution of the product from Preparation 19a (8.00 g, 22.8 mmol) in THF (200 mL) was hydrogenated over RanNi (1.00 g) for 3 hours. The reaction mixture was filtered and concentrated and the residue was dissolved in dioxane (300 mL) and treated with TiCl₃

15 (53 mL of a 1.3 M solution in H₂O). The resulting purple-colored solution was stirred at room temperature until the color was discharged. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution. The resulting suspension was

20 extracted with 1:1 EtOAc/THF and concentrated. The residue was suspended in EtOH and collected to give the title compound as a tan solid (3.50 g, 53%); m.p. 244-250°C.

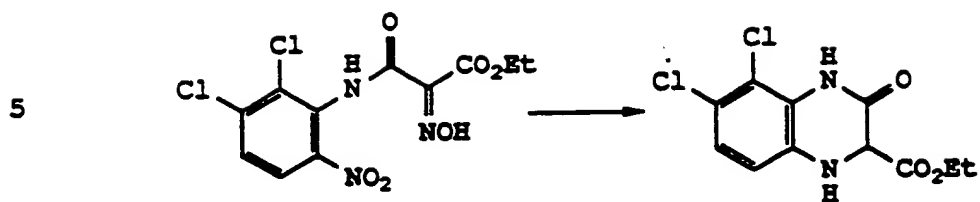
Elemental analysis calculated for C₁₁H₁₁Cl₂N₂O₃:

25 C, 45.70; H, 3.49; N, 9.69.

Found: C, 45.67; H, 3.20; N, 9.53.

-71-

PREPARATION 28a

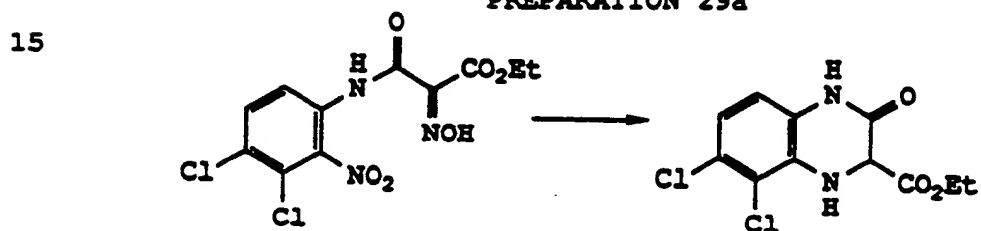


10

Ethyl 5,6-dichloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 20a is converted to the title compound.

PREPARATION 29a



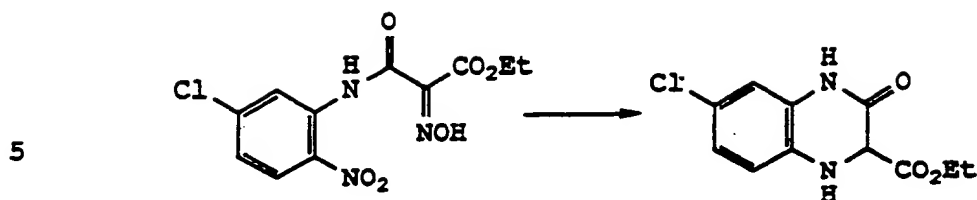
20

Ethyl 7,8-dichloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

In a manner similar to that described in

-72-

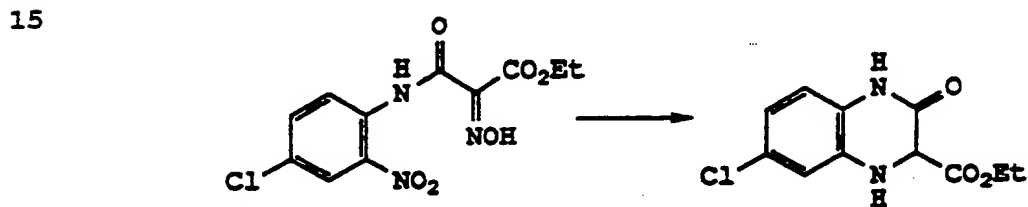
PREPARATION 30a



Ethyl 6-chloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxaline-
carboxylate

10 In a manner similar to that described in Preparation 27a, the product from Preparation 22a is converted to the title compound.

PREPARATION 31a



20

Ethyl 7-chloro-1,2,3,4-tetrahydro-3-oxo-2-quinoxaline-
carboxylate

25 In a manner similar to that described in Preparation 27a, the product from Preparation 23a (8.00 g, 25.3 mmol) is converted to the title compound as a yellow solid (2.11 g, 33%); m.p. 196-198°C.

Elemental analysis calculated for $C_{11}H_{11}ClN_2O_3$:

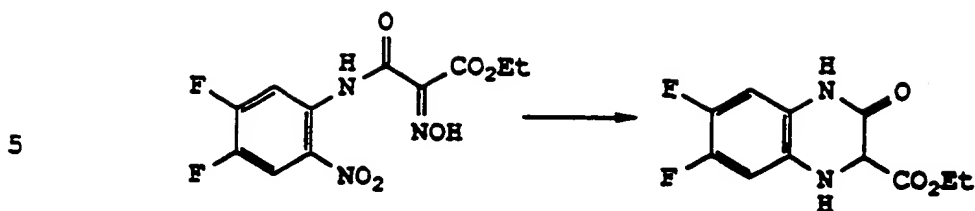
C, 51.88; H, 4.35; N, 11.00; Cl, 13.92

Found: C, 52.05; H, 3.76; N, 10.81; Cl, 14.24.

30

-73-

PREPARATION 32a

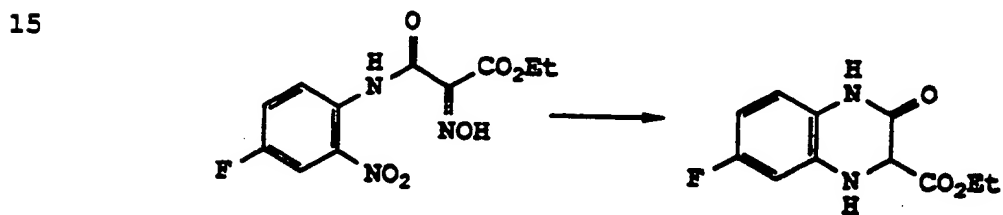


10

Ethyl 6,7-difluoro-1,2,3,4-tetrahydro-3-oxo-2-quinoxalinecarboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 24a is converted to the title compound.

PREPARATION 33a



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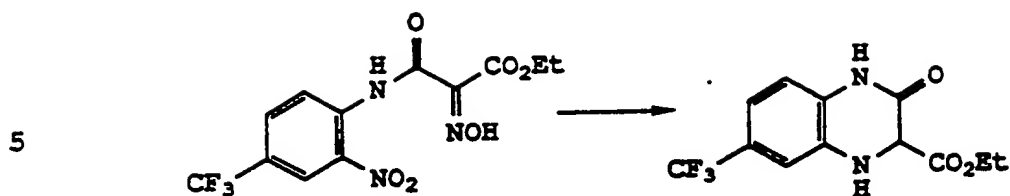
Ethyl 7-Fluoro-1,2,3,4-tetrahydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 27a, the product from Preparation 25a is converted to the title compound.

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-74-

PREPARATION 34a



10

Ethyl 1,2,3,4-tetrahydro-3-oxo-7-(trifluoromethyl)-2-quinoxalinecarboxylate

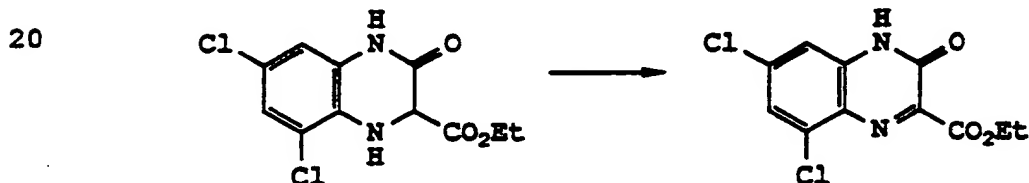
In a manner similar to that described in Preparation 27a, the product from Preparation 26a (8.00 g, 22.9 mmol) is converted to the title compound as a yellow solid (3.39 g, 52%); m.p. 178-180°C.

Elemental analysis calculated for $C_{12}H_{11}F_3N_2O_3$:

15 C, 50.01; H, 3.85; N, 9.72.

Found: C, 50.29; H, 3.52; N, 9.35.

PREPARATION 35a



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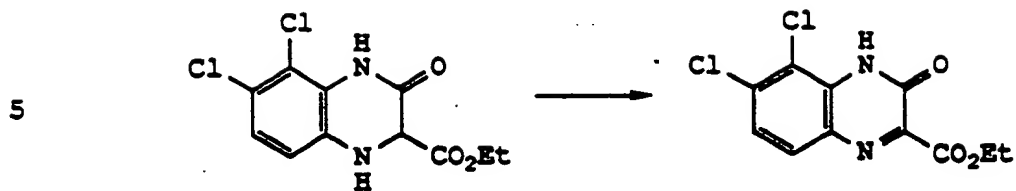
Ethyl 6,8-dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylate

A solution of the product from Preparation 27a (1.00 g, 3.46 mmol) in THF (150 mL) was treated with bromine (3.5 mL of a 1M solution in CH_2Cl_2). The reaction mixture was stirred for 30 minutes and concentrated to give the title compound as a yellow solid (0.98 g, 98%).

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-75-

PREPARATION 36a



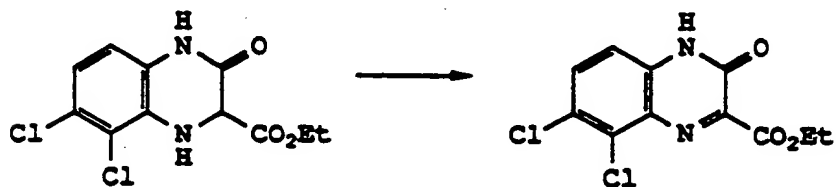
10

Ethyl 5,6-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 28a is converted to the title compound.

PREPARATION 37a

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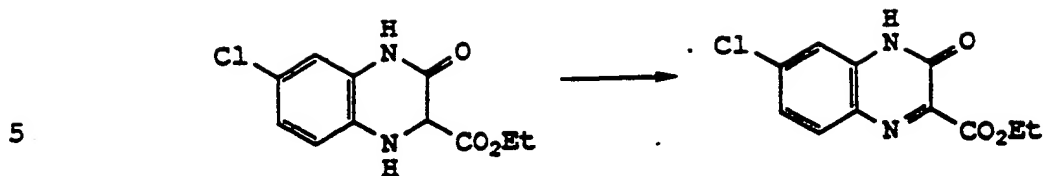
Ethyl 7,8-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 29a is converted to the title compound.

25

-76-

PREPARATION 38a



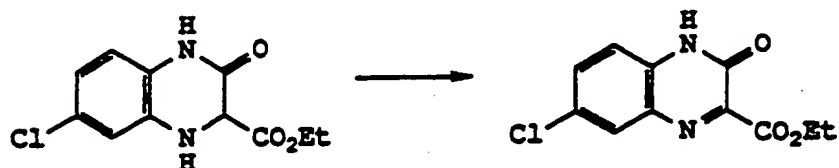
10

Ethyl 6-chloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 30a is converted to the title compound.

PREPARATION 39a

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Ethyl 7-chloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

25

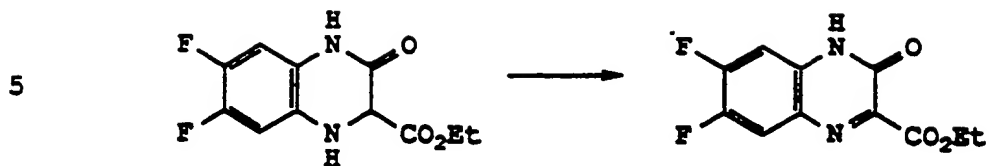
A solution of the product from Preparation 31a (0.50 g, 1.96 mmol) in dioxane (15 mL) was treated with DDQ (0.47 g, 2.06 mmol). The reaction was stirred at room temperature for 15 minutes and filtered. The filtrate was concentrated and crystallized from hot EtOH. The solid which formed on cooling was collected by suction filtration to give

30

the title compound as a yellow solid (0.43 g, 87%).

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PREPARATION 40a

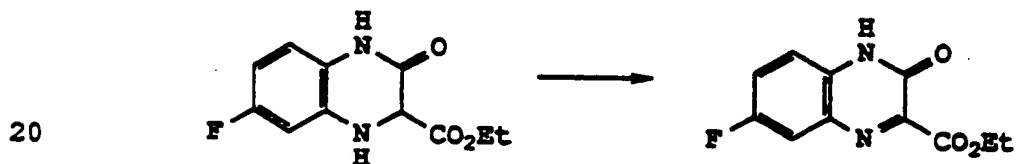


10 Ethyl 6,7-difluoro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 32a is converted to the title compound.

15

PREPARATION 41a

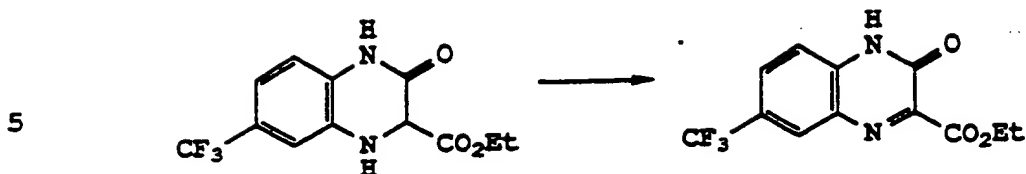


25 Ethyl 7-fluoro-3,4-dihydro-3-oxo-2-quinoxaline-carboxylate

In a manner similar to that described in Preparation 39a, the product from Preparation 33a is converted to the title compound.

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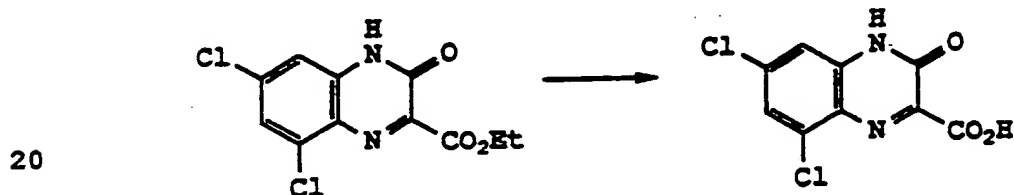
PREPARATION 42a



Ethyl 3,4-dihydro-3-oxo-7-(trifluoromethyl)-2-quinoxalinecarboxylate

10 In a manner similar to that described in Preparation 39a, the product from Preparation 34a (0.50 g, 1.73 mmol) is converted to the title compound as a tan solid (0.32 g, 65%).

PREPARATION 43a

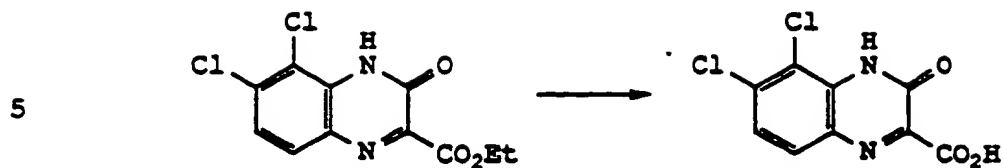


6,8-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

25 In a manner similar to that described in Preparation 7a, the product from Preparation 35a is converted to the title compound.

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PREPARATION 44a



10

5,6-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 36a is converted to the title compound.

PREPARATION 45a

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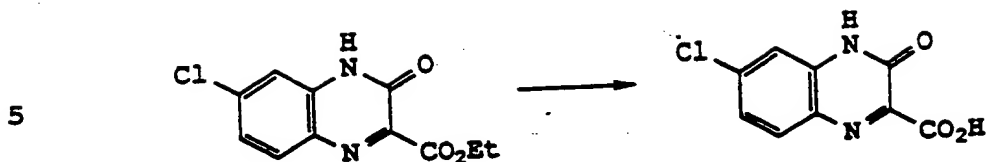
25

7,8-Dichloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 37a is converted to the title compound.

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PREPARATION 46a

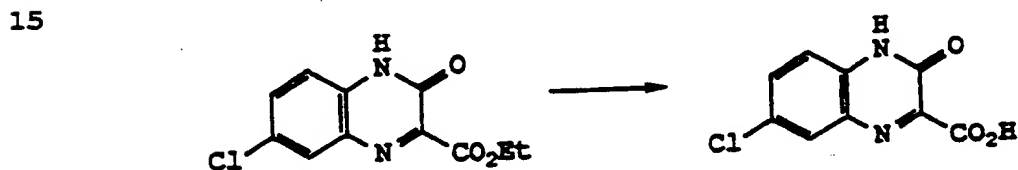


10

6-Chloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 38a is converted to the title compound.

PREPARATION 47a



20

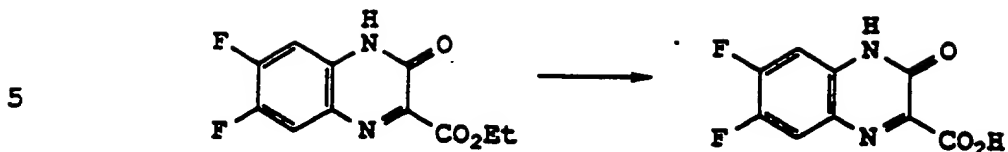
7-Chloro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

25

In a manner similar to that described in Preparation 7a, the product from Preparation 39a is converted to the title compound.

-81-

PREPARATION 48a



10

6,7-Difluoro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 40a is converted to the title compound.

PREPARATION 49a

15



20

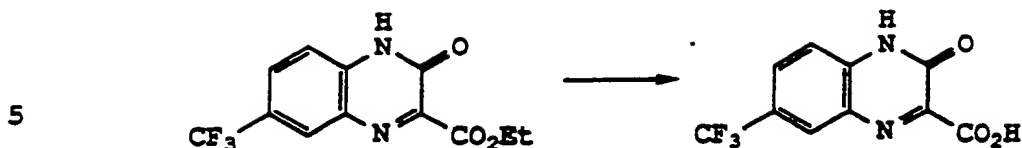
7-Fluoro-3,4-dihydro-3-oxo-2-quinoxalinecarboxylic acid

25

In a manner similar to that described in Preparation 7a, the product from Preparation 41a is converted to the title compound.

-82-

PREPARATION 50a

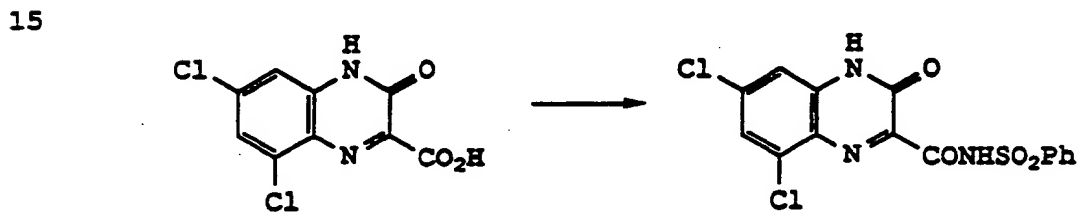


10

3,4-Dihydro-3-oxo-7-(trifluoromethyl)-2-quinoxaline-
carboxylic acid

In a manner similar to that described in Preparation 7a, the product from Preparation 42a is converted to the title compound.

EXAMPLE 48



20

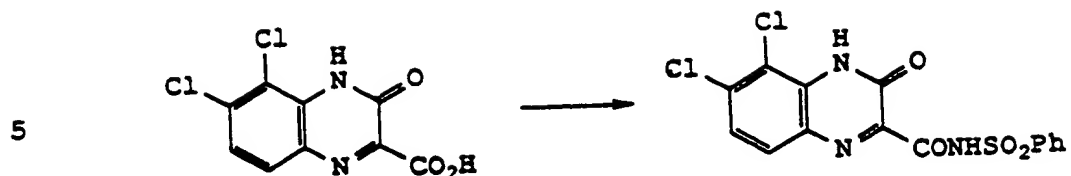
6,8-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-
quinoxalinecarboxamide

25

In a manner similar to that described in Preparation 10a, the product from Preparation 43a is converted to the above compound.

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EXAMPLE 49

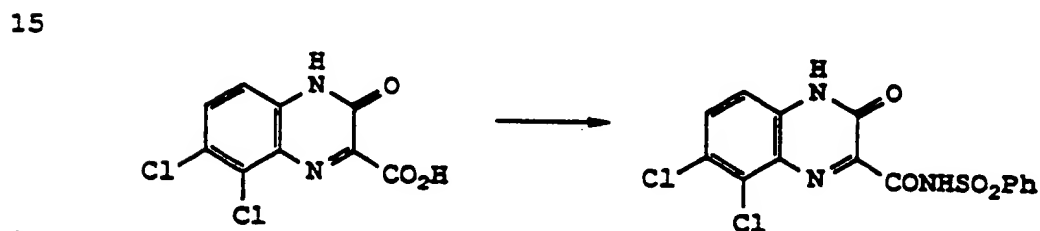


10

5,6-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 44a is converted to the above compound.

EXAMPLE 50



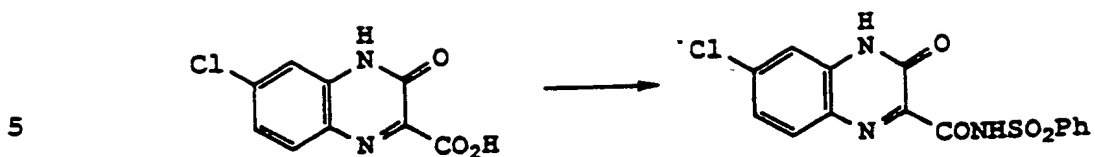
25

7,8-Dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 45a is converted to the above compound.

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EXAMPLE 51



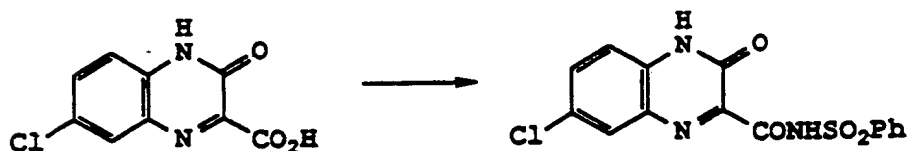
10

6-Chloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 46a is converted to the above compound.

EXAMPLE 52

15



20

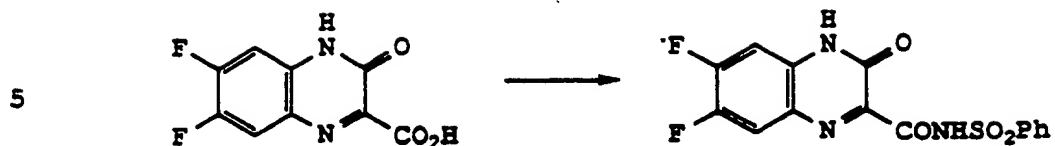
7-Chloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 47a is converted to the above compound.

25

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EXAMPLE 53



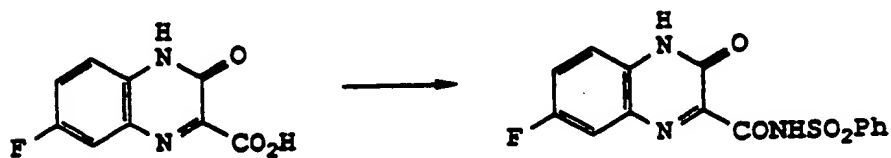
10

6,7-Difluoro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 48a is converted to the above compound.

EXAMPLE 54

15



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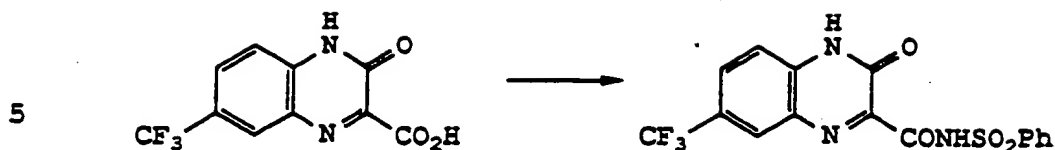
7-Fluoro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 49a is converted to the above compound.

25

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EXAMPLE 55



10

3,4-Dihydro-3-oxo-N-(phenylsulfonyl)-7-(trifluoro-
methyl)-2-quinoxalinecarboxamide

In a manner similar to that described in Preparation 10a, the product from Preparation 50a is converted to the above compound.

BIOLOGICAL TESTING

15

Specifically, the compounds of the present invention have activity as antagonists at the strychnine insensitive glycine receptor which is located on the NMDA receptor complex. As such, the

20

compounds of the present invention are NMDA receptor antagonists. Also, the compounds of the present invention have activity as AMPA and kainate receptor antagonists.

For example, compounds of the invention exhibit

25

valuable biological properties because of these excitatory amino acid antagonizing properties.

The glycine binding assay is performed as described by W. Frost White, et al, Journal of Neurochemistry 1989;53(2):503-12.

30

Selected compounds having the Formula I of the present invention are tested in the glycine binding assay and provide the following data expressed as % inhibition at the dose expressed as molar concentration.

35

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TABLE I
(Pag 1 of 2)

	Example No.	Molar Conc.	% Inhibition
	1	1.00E-4	89
5	2	5.00E-5	23
	3	1.00E-4	38
	4	1.00E-4	71
	6	1.00E-4	55
	9	1.00E-4	73
10	10	1.00E-4	40
	11	1.00E-4	85
	12	5.00E-6	53
	13	1.00E-4	55
	14	1.00E-4	64
15	16	1.00E-4	91
	17	1.00E-4	92
	18	1.00E-4	18
	19	1.00E-4	94
	21	5.00E-5	29
20	22	5.00E-5	25
	23	1.00E-4	36
	24	1.00E-4	68
	25	5.00E-5	90
	26	5.00E-5	75
25	27	1.00E-4	42
	28	1.00E-4	72
	29	1.00E-4	88
	31	1.00E-4	100

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TABLE I
(Page 2 of 2)

	Example No.	Molar Conc.	% Inhibition
5	32	1.00E-4	76
	33	1.00E-5	76
	34	1.00E-4	81
	35	1.00E-4	83
	36	5.00E-4	100
10	37	5.00E-5	100
	38	1.00E-4	83
	40	5.00E-5	90
	41	1.00E-4	34
	42	1.00E-4	86
15	43	1.00E-4	36
	44	1.00E-4	82
	45	5.00E-5	100
	46	5.00E-4	100

20 Additionally selected intermediates of the present invention also provide inhibition in the glycine-binding assay as follows:

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TABLE II

Preparation No.	Molar Conc.	% Inhibition
1	1.11E-4	30
2	1.00E-4	6
3	1.00E-4	97
5	1.00E-4	88
6	1.00E-4	10
7	1.00E-4	13
8	1.00E-4	0
9	1.00E-4	74
10	1.00E-4	65
11	1.00E-4	23

15

The AMPA binding assay may also be performed to provide an activity profile for the compounds of the present invention.

20

The kainate binding assay is performed as described by T. Honore et al, Neuroscience Letters 1986;65:47-52.

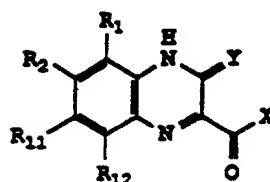
25

Therefore, the compounds of Formula I and their pharmacologically acceptable acid addition salts are effective agents in the prophylaxis and/or therapeutic treatment of disorders responsive to agents which block NMDA receptors, thus forming a further aspect of the present invention in like manner.

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CLAIMS

1. A compound of the formula



or a pharmaceutically acceptable base or acid addition salt thereof; wherein

- 5 (1) Y is oxygen or sulfur;
- (2) R_1 , R_2 , R_{11} , and R_{12} are independently hydrogen, lower alkyl, halogen, trifluoromethyl, cyano, nitro, methylthio, lower alkenyl, lower alkynyl, SO_2NH_2 , $S(O)_{1-2}R$ wherein R is hydrogen or lower alkyl, OCF_3 , or two of R_1 , R_2 , R_{11} , and R_{12} can be taken together to form a carbocyclic ring of six carbons, or can be taken together to form a heterocyclic or heteroaryl ring wherein the heteroatom is oxygen, sulfur, or nitrogen, and wherein the carbon on the carbocyclic ring is optionally further substituted by one of R_1 , R_2 , R_{11} , or R_{12} ;

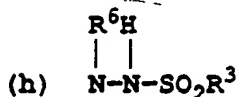
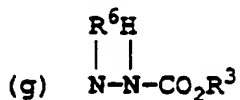
(3) X is

- (a) $NR^6SO_2R^3$,
- 20 (b) NR^6R^3 with the proviso that one of R^6 and R^3 must be other than hydrogen and at the same time one of R_1 , R_2 , R_{11} , and R_{12} must be other than hydrogen,
- (c) NR^6OR^3 ,
- 25 (d) $NR^6CONR^3R^4$ with the proviso that one of R^3 and R^4 must be other than hydrogen,
- (e) NR^6COR^5 ,

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30



35

- (i) an amino acid residue which is
phenylglycine, phenylalanine, alanine,
leucine, isoleucine, proline, or valine,
(j) lower alkyl esters of the amino acid
residue as defined above;

40

wherein

- i) R^3 and R^4 are independently
1) hydrogen;
2) alkyl of from one to
twenty carbons, preferably one to
45 twelve carbons;
3) alkenyl of from three to
twenty carbons, preferably three
to twelve carbons;
4) alkynyl of from three to
50 twenty carbons, preferably three
to twelve carbons;
5) aryl which is phenyl,
indenyl, or naphthyl wherein
phenyl is
55 aa) unsubstituted or
bb) substituted by one to
five of lower alkyl or
halogen, or
cc) substituted by one to
60 three of
xxi) trifluoromethyl,
xxii) nitro,
xxiii) amino,

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- 65 xxiv) mono- or di-lower
alkylamino,
xxv) hydroxy,
xxvi) lower alkoxy,
xxvii) carboxy, or
xxviii) NHCOR^5 wherein R^5
70 is independently as
defined below,
- xxix) $\begin{array}{c} \text{O} \\ | \\ \text{NHCOAlk}_{1-6} \end{array}$ wherein
75 Alk_{1-6} is lower alkyl,
xxx) NHSO_2R^5 wherein R^5
is independently as
defined herein,
xxxi) CN,
80 xxxii) CONR^5R^6 wherein R^5
and R^6 are independently
as defined herein,
xxxiii) $\text{S(O)}_{0-2}\text{R}^5$ wherein
85 R^5 is independently
defined herein,
- xxxiv) $\begin{array}{c} \text{O} \\ | \\ -\text{CR}^5; \end{array}$
- 6) arylloweralkyl;
90 7) arylloweralkenyl;
8) heterocycle;
9) heteroaryl;
10) $(\text{CH}_2)_q\text{R}^7$ wherein q is an
integer of one to four and R^7 is
95 (A) heterocycle,
(B) heteroaryl,
(C) SO_2R^8 wherein R^8 is
hydrogen or lower alkyl and R

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- 100 is independently as defined herein,
- (D) PO_3R^8 wherein R^8 is as defined above,
- (E) CO_2R^8 wherein R^8 is as defined above, or
- 105 (F) NR^9R^{10} wherein R^9 and R^{10} are independently hydrogen or alkyl or R^9 and R^{10} are taken together to form a heteroaryl ring; or
- 110 11) an amino acid residue as defined above;
- ii) R^5 is
- 1) hydrogen,
- 115 2) lower alkyl,
- 3) lower alkenyl,
- 4) aryl,
- 5) arylloweralkyl,
- 6) arylloweralkenyl,
- 120 7) heteroaryl or
- 8) heteroarylloweralkyl;
- iii) R^6 is
- 1) hydrogen or
- 2) lower alkyl, preferably
- 125 hydrogen.

2. A compound of Claim 1 wherein R_1 and R_{12} are hydrogen and R_2 and R_{11} are chloro.
3. A compound of Claim 1 wherein X is $\text{NR}^6\text{SO}_2\text{R}^3$.
4. A compound of Claim 1 wherein X is NR^6R^3 .
5. A compound of Claim 1 wherein X is NR^6OR^3 .

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6. A compound of Claim 1 wherein X is $\text{NR}^6\text{CONR}^3\text{R}^4$.
7. A compound of Claim 1 wherein X is NR^6COR^5 .
8. A compound of Claim 1 wherein X is $\text{NR}^6\text{CO}_2\text{R}^3$.
9. A compound of Claim 1 wherein X is $\text{NHNHSO}_2\text{R}^3$.
10. A compound of Claim 1 wherein X is $\text{NHNHCO}_2\text{R}^3$.
11. A compound of Claim 4 which is α -[[6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaliny]carbonyl]amino-(\pm)-benzeneacetic acid.
12. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxaline-carboxamide.
13. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-3-oxo-N-(phenylsulfonyl)-2-quinoxaline-carboxamide.
14. A compound of Claim 3 which is N-(butylsulfonyl)-6,7-dichloro-3,4-dihydro-3-oxo-2-quinoxaline-carboxamide.
15. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(4-methylphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.
16. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(2-chloro-5-nitrophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.

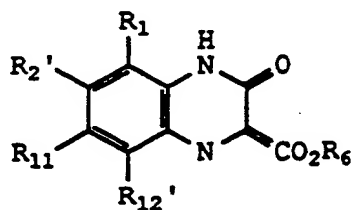
-95-

17. A compound of Claim 3 which is 6,7-dichloro-N-[(4-chloro-2-nitrophenyl)sulfonyl]-3,4-dihydro-3-oxo-2-quinoxalinecarboxamide.
18. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-(2-thionylsulfonyl)-3-oxo-2-quinoxalinecarboxamide.
19. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(4-methoxyphenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.
20. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-3-oxo-N-[[5-(2-pyridinyl)-2-thienyl]-sulfonyl]-2-quinoxalinecarboxamide.
21. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-N-[(3-chlorophenyl)sulfonyl]-3-oxo-2-quinoxalinecarboxamide.
22. A compound of Claim 3 which is 6,7-dichloro-3,4-dihydro-3-oxo-N-[(3-nitrophenyl)sulfonyl]-2-quinoxalinecarboxamide.
23. A compound of Claim 3 which is 6,8-dichloro-3,4-dihydro-N-(methylsulfonyl)-3-oxo-2-quinoxalinecarboxamide.
24. A compound of Claim 3 which is 6,8-dichloro-3,4-dihydro-3-oxo-N-phenylsulfonyl)-2-quinoxalinecarboxamide.
25. A pharmaceutical composition comprising a therapeutically effective amount of a compound of

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Claim 1 together with a pharmaceutically acceptable carrier.

26. A method for treating cerebrovascular disorders which comprises administering to a patient in need thereof the pharmaceutical composition of Claim 25 in unit dosage form.
27. A method for treating disorders responsive to the blockade of glutamic and aspartic acid receptors which comprises administering to a patient in need thereof the pharmaceutical composition of Claim 25 in unit dosage form.
28. A method for treating stroke which comprises administering to a patient in need thereof the pharmaceutical composition of Claim 26 in unit dosage form.
29. A pure compound of the Formula XII

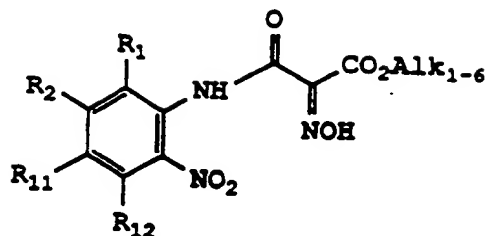


XII

R_1 and R_{11} are defined above in Claim 1 and R_6 is hydrogen or lower alkyl and R'_2 and R'_{12} are independently halogen or hydrogen with the proviso that one of R'_2 and R'_{12} is halogen.

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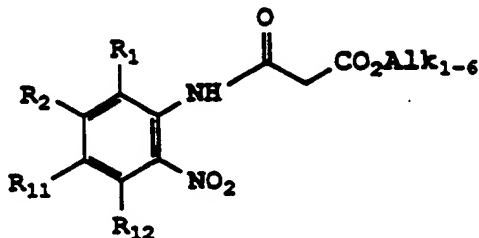
30. A compound of the formula (V)



V

wherein R_1 , R_2 , R_{11} , and R_{12} are as defined in Claim 1 and Alk_{1-6} is lower alkyl.

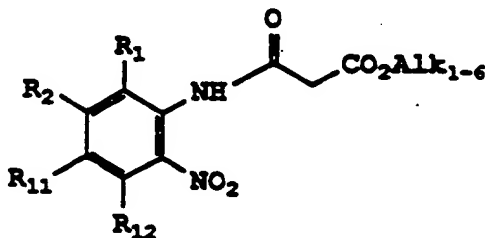
31. A compound of the Formula (VI)



VI

wherein R_1 , R_2 , R_{11} , and R_{12} are as defined in Claim 1 and Alk_{1-6} is lower alkyl.

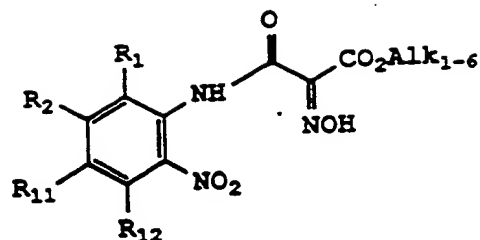
32. A method of 1) treating a compound of the Formula (VI)



VI

with sodium nitrite to obtain a compound of the Formula (V)

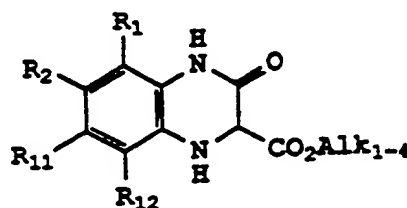
-98-



V

then 2) treating the compound of the Formula II'2
with hydrogen over Raney nickel followed by
treatment with TiCl_3 to obtain a compound of the
Formula (IV)

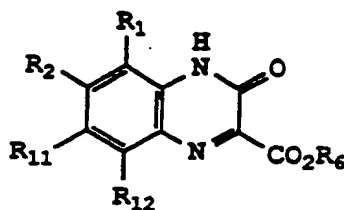
10



IV

with the compound of the Formula IV further
3) reacted with Br_2 , n-bromosuccinimide, NaOCl ,
or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and
alternatively saponifying this product to obtain
the compound of the Formula (II)

15

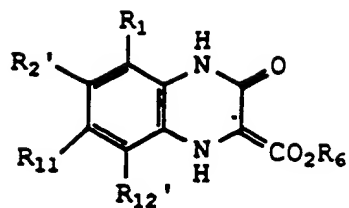


II

wherein R_1 , R_2 , R_{11} , R_{12} , and R_6 are as defined in
Claim 1.

33. A pure compound of the Formula (XIII)

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XIII

wherein R_1 , R_2' , R_{11} , R_{12}' , and R_6 are as defined in Claim 29.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 91/08586

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ⁶		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl.5	C 07 D 241/44	C 07 D 401/04
C 07 C 251/38	A 61 K 31/495	C 07 C 233/54
II. FIELDS SEARCHED		
Minimum Documentation Searched ⁷		
Classification System	Classification Symbols	
Int.Cl.5	C 07 D 241/00 C 07 C 251/00	C 07 D 401/00 A 61 K 31/00
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸		
III. DOCUMENTS CONSIDERED TO BE RELEVANT⁹		
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³
A	EP,A,0008864 (FISONS LTD) 19 March 1980, see claims 1,5,8,9 ----	1,25,32
A	EP,A,0010426 (ELI LILLY AND CO.) 30 April 1980, see claims 1,4,6 (cited in the application) ----	1,25,32
A	US,A,4252954 (ABDULLA et al.) 24 February 1981, see claims 1,8 (cited in the application) ----	1,25
A	US,A,4264600 (ABDULLA) 28 April 1981, see claim 1, reaction schemes 1,2 (cited in the application) -----	1,25,30 ,32
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>¹⁰ Special categories of cited documents:</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> </div> <div style="width: 45%;"> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"A" document member of the same patent family</p> </div> </div>		
IV. CERTIFICATION		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
18-02-1992		31.03.92
International Searching Authority		Signature of Authorized Officer
EUR PEAN PATENT OFFICE		 T. MORTENSEN

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claim numbers 26-28 because they relate to subject matter not required to be searched by this Authority, namely:
See PCT Rule 39.1(iv): method for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.
2. ☐ Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:
3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this International application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this International search report covers only those claims of the International application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
☐ No protest accompanied the payment of additional search fees.

ANHANG
zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

ANNEX
to the International Search
Report to the International Patent
Application No.

ANNEXE
au rapport de recherche inter-
national relatif à la demande de brevet
international n°

PCT/US91/08586 SAE 54229

In diesem Anhang sind die Mitglieder
der Patentfamilien der im obenge-
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